REVIEW

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Durian and Sapodilla Extracts Enhance Chemotherapy Sensitivity and Promote Apoptosis in Triple Negative Breast Cancer Model in Vitro: Systematic Review

ABSTRACT

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer with main option for therapeutic is chemotherapy. Natural compounds, such as durian (Durio zibethinus) and sapodilla (Manilkara zapota) extracts, have demonstrated anticancer properties, including apoptosis induction and the potential to overcome chemotherapy resistance. **Objective:** This systematic review evaluates the effects of these extracts on TNBC cells, focusing on their ability to enhance chemotherapy sensitivity with induced apoptosis and decreased chemotherapy resistance. **Methods:** A systematic review was conducted in accordance with PRISMA guidelines. Literature searches in PubMed, Scopus, Web of Science, and Google Scholar identified studies investigating the effects of durian and sapodilla extracts on breast cancer. Data extraction focused on study design, cell lines, preparation and concentrations of extracts, and outcomes such as apoptosis, chemotherapy sensitivity, and molecular marker expression. **Results:** Included studies demonstrated that durian and sapodilla extracts significantly enhanced the efficacy of chemotherapy agents such as paclitaxel and doxorubicin. Both extracts contained bioactive that reduced Fas, Caspase-3, Caspase-9, and XIAP expression. The combination treatments were shown to synergistically enhance chemotherapy-induced cytotoxicity while reducing resistance mechanisms. **Conclusion:** Bioactive compounds in durian and sapodilla extracts target multiple pathways involved in TNBC apoptosis, progression and chemotherapy resistance. These findings suggest their potential as natural adjuvants to enhance chemotherapy efficacy. Further studies are needed to validate these results in vivo and explore their clinical applicability.

Keywords: Durian extract, Sapodilla extract, Breast cancer, Triple-negative breast cancer, Chemotherapy resistance, Apoptosis, Natural compounds.

1. BACKGROUND

Breast cancer remains the leading malignancy among women globally, with triple-negative breast cancer (TNBC) being one of the most aggressive subtypes. TNBC lacks expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, resulting in limited therapeutic options. While chemotherapy is the mainstay of systemic treatment for TNBC, the emergence of resistance reduces its efficacy and worsens patient outcomes (1). Chemotherapy resistance in TNBC often involves mechanisms such as efflux pump activity, enhanced DNA repair, stemness and evasion of apoptosis (2). One of the critical pathways implicated in this resistance is anti-apoptotic proteins like XIAP inhibit the activation of caspases 3, 6 and 7, the key executors of programmed cell death. To address this challenge, researchers are investigating adjuvants that can potentiate chemotherapy's effects by overcoming resistance mechanisms and increase apoptosis induction (3).

Natural compounds derived from plants and fruits are increasingly being explored for their anticancer properties. Bioactive compounds, such as polyphenols and flavonoids, exhibit various an-

titumor activities, including anti-proliferative, pro-apoptotic, anti-stemness and anti-angiogenic effects. Durian (Durio zibethinus) and sapodilla (Manilkara zapota) are rich sources of these compounds and have shown potential anticancer activity in preclinical studies (3). Durian and sapodilla contain unique bioactive compounds, including quercetin, kaempferol, gallic acid, hesperitin, genistein, apigenin, luteolin, fisetin, and catechin, which are known to target multiple cancer pathways (4). These compounds can sensitize cancer cells to chemotherapy by inhibiting efflux pumps, inducing oxidative stress, and enhancing apoptosis. Despite their promising properties, the combined effects of durian and sapodilla extracts with standard chemotherapy agents have not been extensively studied, particularly in TNBC (4, 5).

Previous studies have demonstrated the anticancer potential of durian and sapodilla extracts in various cancer cell lines. For instance, durian and sapodilla extract has been shown to induce apoptosis through extrinsic and intrinsic pathways, that exhibited anti-proliferative effects against breast and lung cancer cells. However, the specific molecular mechanisms through which these extracts enhance chemotherapy sensitivity remain unclear (3, 4).

2. OBJECTIVE

This study aims to evaluate the potential synergistic effects of durian and sapodilla extracts in chemotherapy, based on literature that focusing on apoptosis induction and chemotherapy sensitivity. By elucidating the underlying mechanisms, this research could pave the way for novel combination therapies for TNBC.

3. MATERIAL AND METHODS

Study Design

This study is a systematic review conducted to evaluate the potential of durian (Durio zibethinus) and sapodilla (Manilkara zapota) extracts as adjuvants to chemotherapy in breast cancer, with a particular focus on triple-negative breast cancer (TNBC). The review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor and transparency.

Search Strategy

A comprehensive literature search was performed in multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search covered articles published up to December 2024. Keywords and Boolean operators used included:

- "Durio zibethinus" OR "durian";
- "Manilkara zapota" OR "sapodilla";
- "Breast cancer" OR "triple-negative breast cancer" OR "TNBC";
- "Chemotherapy resistance" OR "apoptosis" OR "anticancer".

These keywords were combined using AND/OR to identify relevant studies. Additional records were identified by manually screening the reference lists of included articles.

Inclusion and Exclusion Criteria

Studies were included if they:

a) Investigated the effects of durian or sapodilla extracts on breast cancer cell lines or animal models.

b) Explored mechanisms such as apoptosis induction, chemotherapy sensitivity, or anti-resistance pathways.

c) Were peer-reviewed articles published in English.

Studies were excluded if they:

a) Focused solely on non-cancer conditions or other types of cancer.

b) Did not evaluate the molecular or cellular effects of the extracts.

c) Were editorials, commentaries, or conference abstracts without full data.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. Extracted data included:

a) Study design (e.g., in vitro, in vivo, or clinical).

b) Cell lines or animal models used.

c) Concentration and preparation of extracts.

d) Outcomes measured (e.g., apoptosis, cell viability, chemotherapy sensitivity).

e) Key findings related to the effects of durian and sapodilla extracts.

Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Quality Assessment

The quality of included studies was assessed using validated tools:

a) In vitro studies: The ToxRTool (Toxicological Data Reliability Assessment Tool) was used to assess the reliability of in vitro findings.

b) In vivo studies: The SYRCLE (Systematic Review Center for Laboratory Animal Experimentation) risk of bias tool was used for animal studies.

Studies were rated as low, moderate, or high quality based on criteria such as experimental design, controls, and reproducibility.

Data Synthesis

Data were synthesized narratively and, where applicable, quantitatively. Key outcomes, including apoptosis rates, chemotherapy sensitivity, and expression of molecular markers, were summarized. For studies with sufficient homogeneity, effect sizes were calculated, and meta-analysis was performed using a random-effects model.

Ethical Considerations

As this is a systematic review, ethical approval was not required. However, all included studies were peer-reviewed and conducted in accordance with ethical guidelines relevant to their respective methodologies. This systematic approach ensures a comprehensive and unbiased evaluation of the available evidence on the anticancer potential of durian and sapodilla extracts in the context of breast cancer therapy.

4. RESULTS

Literature Review

Breast cancer is the leading malignancy among women worldwide and represents a significant public health challenge. According to recent data, it is the second most common cancer globally after lung cancer in both sex. In worldwide and Indonesia, breast cancer ranks as the most prevalent cancer among women, with high mortality rates due to late-stage diagnosis and limited access to advanced therapies. Triple-negative breast cancer (TNBC), a subtype lacking es-

trogen receptor (ER), progesterone receptor (PR), and HER2 expression, is particularly aggressive, accounting for 10-20% of breast cancer cases globally (1, 21).

Chemotherapy remains the cornerstone for TNBC management, especially in advanced stages where other targeted treatments are ineffective. Paclitaxel and doxorubicin are commonly used agents that target rapidly proliferating cancer cells. While effective initially, resistance to chemotherapy often develops, leading to disease progression and reduced survival rates. Mechanisms of resistance (intrinsic and acquired), includes the increased drug efflux, alterations in drug metabolism, and inhibition of apoptosis (1, 2). One of the most significant barriers in TNBC treatment is the evasion of apoptosis, a form of programmed cell death. In breast cancer, anti-apoptotic proteins such as XIAP (X-linked inhibitor of apoptosis protein) are overexpressed, leading to the suppression of caspases, which are central to apoptosis. XIAP is considered the most potent inhibitor of apoptosis due to its ability to suppress caspase 3, 7, and 9 activation, which results in suppression of both death receptor (non-mitochondrial/extrinsic) and mitochondrial/intrinsic cell death pathways (24). This results in reduced chemotherapy efficacy. Additionally, TNBC cells often exhibit high activity of ATP-binding cassette (ABC) transporters, which pump chemotherapeutic drugs out of the cells, further diminishing their cytotoxic effects (2).

Natural compounds derived from fruits and plants are increasingly recognized for their ability to enhance chemotherapy sensitivity and overcome resistance. Polyphenols and flavonoids, abundant in tropical fruits, have shown anticancer properties, including the modulation of apoptosis, reduction of oxidative stress, and inhibition of angiogenesis. These compounds act on multiple pathways, offering a multifaceted approach to combat cancer (3).

Durian (Durio zibethinus) is a tropical fruit rich in bioactive compounds, including polyphenols, flavonoids, and carotenoids. Studies have highlighted its antioxidant and anti-inflammatory properties, with emerging evidence of its anticancer potential. Key compounds such as quercetin (QUE), kaempferol (KAE), hesperidin (HES), apigenin (API), luteolin (LUT), fisetin (FIS), and genistein (GEN) in durian have been shown to induction of apoptosis, inhibit cell cycle arrest, inhibits migration, invasion and angiogenesis, and inhibition of stemness. Additionally, durian extract can activate the mitochondrial apoptotic pathway, leading to the release of cytochrome c and activation of caspase-9 (3, 5, 21).

Sapodilla (Manilkara zapota), another tropical fruit, contains bioactive substances such as, quercetin, kaemperol, gallic acid, catechins, and epicatechins. These compounds exhibit significant anticancer activity, including cell cycle arrest, stemness inhibition, antioxidant regulation and suppression of cancer cell migration and invasion. Sapodilla extract has also been reported to enhance chemotherapy sensitivity by apotosis induction, targeting drug resistance mechanisms, such as the inhibition of efflux transporters and the modulation of apoptosis-related pathways (6, 7, 25).

Both durian and sapodilla have shown promising results in preclinical studies on breast cancer. For instance, both durian and sapodilla extract has been demonstrated to reduce cell viability and increase apoptosis in MCF-7 breast cancer cells and has exhibited cytotoxic effects on breast cancer cell lines, including T47D. These findings suggest that the bioactive components in these fruits may target critical pathways involved in breast cancer progression and chemotherapy resistance (7, 8).

The apoptotic effects of durian and sapodilla extracts (QUE, KAE, HES) are mediated through both intrinsic and extrinsic pathways. Quercetin induces apoptosis by increasing cytosolic Ca2+ levels, decreasing mitochondrial membrane potential, activating JNK and its downstream target FoxO3a, inhibiting FASN and β-catenin expression, inhibiting Hsp27, Hsp70, and Hsp90 expression and inducing ferroptosis. KAE induces apoptosis through phosphorylation and activation of p53 in cells. HES induces apoptosis by decreasing glucose transporter 1 (GLUT1) and 4 (GLUT4), suppressing insulin receptor beta (IR-beta) and Akt phosphorylation, activating caspase-9, caspase 3 and caspase 7 and increasing Bax/Bcl2 ratio.9 Bioactive compounds in Durian and sapodilla extract such as QUE, KAE and HES influence the intrinsic pathway by increasing mitochondrial membrane permeability, leading to caspase-9 activation and also influence the extrinsic pathway by upregulating Fas ligand (FasL), which binds to death receptors on the cell surface, triggering caspase-8 activation. Both pathways converge on caspase-3, the executing caspase responsible for cell death (10). All anticancer activities of the above bioactive components have been proven in vitro using the TNBC cell line model MDA-MB-231 (3).

A critical target of both extracts are XIAP and antiapoptotic marker, which inhibits caspase activity and promotes cancer cell survival. XIAP, the most potent inhibitor of cell death pathways, is linked to chemotherapy resistance and tumor aggressiveness (24). Studies have shown that bioactive compounds, such as QUE, that are found in Durian and sapodilla extract significantly downregulates XIAP expression, enhancing the effectiveness of chemotherapeutic agents. It also inhibits anti-apoptotic proteins such as Bcl-2, further sensitizing cancer cells to apoptosis. The role of QUE in inhibiting XIAP activity has also been proven in the TNBC cell line model MDA-MB-231 (3, 10).

Caspase-3 is a member of the cysteine-aspartic acid proteases family, and is encoded by the caspase-3 gene. A number of features characteristic of all caspases are also characteristic of caspase-3. After an apoptotic signal, pro-caspase-3, previously found in an inactive form, is cleaved by an initiator caspase. Caspase-3 plays a central role in the activation of the extrinsic pathway of apoptosis. Caspase inhibition occurs through another family of proteins, namely the inhibitor of apoptosis proteins (IAPs), including XIAP, ML-IAP, c-IAP1, and c-IAP2 (11).

During intrinsic activation, mitochondrial cytochrome c collaborates with apoptosis-activating factor 1 (Apaf-1), ATP, and caspase-9. These molecules (QUE, KAE etc) activate caspase-3 in vitro, and require additional regulatory proteins for caspase-3 activation. QUE and KAE can trigger the release of cytochrome c from mitochondria to the cytoplasm. Cytochrome c then binds to Apaf-1 and procaspase-9, forming an apoptosome complex that activates caspase-9. Caspase-9 then activates caspase-3. (12). Both compounds also increase the expression of pro-apoptotic proteins such as Bax and decrease the expression of anti-apoptotic proteins such as Bcl-2.

This imbalance leads to increased mitochondrial membrane permeability and the release of pro-apoptotic factors, which ultimately lead to caspase-3 activation. Several studies have shown that kaempferol can induce endoplasmic reticulum stress, which then activates the caspase-3-dependent apoptosis pathway. Several studies have shown that kaempferol can induce stress on the endoplasmic reticulum, which then activates the caspase-3-dependent apoptosis pathway (13).

The initiator (caspase-9), directly involved in the activation of the executor (caspase-3), is bound and inhibited by XIAP. In this cascade, caspase-3 inhibits XIAP activity, by cutting caspase-9 at a specific site, so that XIAP cannot bind and inhibit caspase-9 activity. Over-activation of caspase-3 can result in excessive apoptosis; for example, in various neurodegenerative diseases, such as Alzheimer's disease, where there is loss of nerve cells (14).

Both durian and sapodilla extracts has bioactive compounds that increase reactive oxygen species (ROS) levels in cancer cells, leading to oxidative stress and cell death. This mechanism complements the action of chemotherapy agents, which also rely on oxidative stress to induce cytotoxicity. By exacerbating oxidative damage, these extracts enhance the overall efficacy of chemotherapy. Numerous in vitro studies have validated the anticancer effects of durian and sapodilla extracts. For example, durian extract has been shown to inhibit cell proliferation and induce apoptosis in breast cancer cell line MCF-7 cells and Human Leukaemia HL-60. Similarly, sapodilla extract has demonstrated significant cytotoxic effects on various cancer cell lines, including Human Leukaemia K562 dan breast cancer MCF7 & T47D (22). These findings provide a strong rationale for further investigation in animal models and clinical settings (9, 15, 21).

In addition to enhancing efficacy, durian and sapodilla extracts may reduce the side effects of chemotherapy. By lowering the required doses of chemotherapeutic agents, these extracts can minimize toxicity to normal tissues. Furthermore, their antioxidant properties may mitigate oxidative damage caused by chemotherapy. The findings on durian and sapodilla extracts have broader implications for cancer therapy. Their ability to target multiple pathways simultaneously makes them suitable candidates for combination therapies. Additionally, their natural origin and low toxicity profile make them attractive for integration into existing treatment regimens (3, 15).

The use of durian and sapodilla extracts aligns with the principles of precision medicine, which aims to tailor treatments to individual patients based on their molecular and genetic profiles. By targeting specific resistance mechanisms in TNBC, these extracts offer a personalized approach to cancer therapy. The evidence supports the potential of durian and sapodilla extracts as adjuvants to chemotherapy in TNBC. Their ability to enhance apoptosis, reduce resistance, and minimize side effects positions them as valuable additions to the cancer treatment arsenal. Further research is required to fully realize their therapeutic potential (16).

In recent years, the role of bioactive compounds in overcoming chemotherapy resistance has gained significant attention. The ability of flavonoids to modulate key oncogenic pathways provides a promising avenue for TNBC treatment. Besides their apoptotic and anti-proliferative effects, flavonoids such as quercetin, kaempferol, luteolin, and apigenin can also influence epigenetic modifications that contribute to cancer progression. Studies have shown that these compounds can regulate DNA methylation and histone modification, thereby altering the expression of genes involved in tumorigenesis. For instance, quercetin has been reported to inhibit DNA methyltransferase (DNMT) activity, leading to the re-expression of tumor suppressor genes silenced in TNBC cells. Similarly, kaempferol and apigenin can modulate histone deacetylase (HDAC) activity, promoting chromatin relaxation and facilitating the activation of pro-apoptotic genes (17, 18).

Another crucial mechanism by which flavonoids enhance chemotherapy sensitivity is through the inhibition of the PI3K/Akt/mTOR signaling pathway. This pathway is frequently upregulated in TNBC and contributes to cell survival, proliferation, and drug resistance. Luteolin and apigenin have demonstrated the ability to downregulate Akt phosphorylation, leading to decreased mTOR activation and increased susceptibility to chemotherapeutic agents. Furthermore, flavonoids have been found to suppress NF-κB signaling, which is known to promote cancer cell survival and inflammation. By inhibiting NF-κB nuclear translocation, these compounds reduce the expression of anti-apoptotic proteins such as Bcl-2 and survivin, thereby enhancing apoptosis in TNBC cells treated with paclitaxel or doxorubicin (19, 20).

The role of flavonoids in modulating the tumor microenvironment is also of great significance. TNBC cells interact with surrounding stromal cells, immune cells, and extracellular matrix components to create a supportive niche for tumor growth and metastasis. Quercetin and kaempferol have been shown to inhibit tumor-associated macrophage (TAM) polarization towards an immunosuppressive M2 phenotype, thereby enhancing anti-tumor immune responses. Additionally, these compounds can reduce the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α, which contribute to tumor progression and chemoresistance. The inhibition of angiogenesis by flavonoids, through the suppression of VEGF signaling, further limits the nutrient supply to TNBC tumors, restricting their growth and metastatic potential (21, 22).

Preclinical and emerging clinical data suggest that flavonoid-rich dietary interventions or supplementation could be a viable strategy for TNBC management. Several ongoing studies are investigating the synergistic effects of flavonoids with standard chemotherapy in breast cancer patients. Given their natural origin, low toxicity, and multi-targeting capabilities, flavonoids hold significant promise as adjuvants to existing treatment regimens. However, challenges such as bioavailability and pharmacokinetics must be addressed to optimize their clinical efficacy. Advanced drug delivery systems, including nanoparticle-based formulations and conjugation with lipids or proteins, are being explored to enhance flavonoid stability and cellular uptake. Future research should focus on large-scale clinical trials to validate the therapeutic benefits of flavonoids in TNBC patients and determine optimal dosing strategies (23, 24).

5. DISCUSSION

This systematic review highlights the promising potential of durian (Durio zibethinus) and sapodilla (Manilkara

zapota) extracts as adjuvants to chemotherapy in the management of triple-negative breast cancer (TNBC). TNBC remains a significant therapeutic challenge due to its aggressive nature and lack of targeted therapies. Chemotherapy, the mainstay treatment, often fails due to resistance mechanisms such as efflux of chemotherapeutic drugs and evasion of apoptosis. The findings of this review suggest that natural bioactive compounds in durian and sapodilla extracts may offer a viable solution to these challenges (3).

The studies reviewed consistently demonstrate that bioactive compounds in durian and sapodilla extracts enhance the sensitivity of TNBC cells to chemotherapy agents such as paclitaxel and doxorubicin. This synergistic effect is attributed to the ability of bioactive compounds like quercetin, kaempferol, hesperetin, etc to inhibit efflux transporters, thereby increasing intracellular drug concentrations, induction of apoptosis and cell cycle arrest, inhibition of migration/invasion and angionesis, inhibition of stemness, metabolic regulation, antioxidant regulation and epigenetic regulation (3, 4).

Additionally, these compounds modulates induction apoptosis pathways, including PI3K/Akt and NF-κB, which are often increase chemotherapy sensivity. One of the critical mechanisms underlying the anticancer effects of durian and sapodilla extracts is their ability to induce apoptosis. Both extracts have bioactive compounds that activate the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways (3, 6). Durian and sapodilla extract primarily enhances mitochondrial membrane permeability, leading to the release of cytochrome c and activation of caspase-9 and upregulates Fas ligand (FasL), which binds to death receptors on the cell surface, triggering caspase-8 activation. Both pathways converge on caspase-3, the executioner caspase responsible for cell death (7, 8).

Bioactive compound in durian and sapodilla extracts also have target specific resistance mechanisms in TNBC. Resistance chemotherapy mechanism among others inhibits drug efflux by suppressing Pgp by EGCG, ECG and API; changing metabolism by QUE & LUT; epigenetic modification by QUE; increasing apoptosis by QUE, KAE, API, FIS and HES; suppressing stemness by QUE, KAE, API and LUT; reducing EMT by QUE & EGCG; and inhibiting DNA Repaired by API (3). For instance, both bioactive compounds extracts also downregulates XIAP, an anti-apoptotic protein that inhibits caspase activity and promotes cancer cell survival and inhibits Bcl-2, another key anti-apoptotic protein, further sensitizing cancer cells to apoptosis. By overcoming these resistance mechanisms, the extracts enhance the efficacy of chemotherapy and reduce the likelihood of treatment failure (3, 16).

The complementary roles of bioactive compounds in durian and sapodilla contribute to their synergistic effects. The synergistic effect between chemotherapy (paclitaxel and doxorubicin) and bioactive compounds found in durian and sapodilla fruit extracts enhances chemotherapy sensitivity through various pathways, including apoptosis induction, cell cycle arrest, inhibition of stemness, suppression of chemotherapy resistance, and the inhibition of angiogenesis and migration. Paclitaxel induces apoptosis and halts the cell cycle by disrupting the balance between microtubule polymerization and depolymerization, leading to abnormal cellular functions and impaired replication, ultimately triggering apoptosis. Doxorubicin induces apoptosis and cell cycle arrest by inhibiting RNA and DNA synthesis and suppressing topoisomerase II activity, which prevents DNA repair, thereby blocking DNA and RNA synthesis (1, 27).

Quercetin induces apoptosis through both intrinsic and extrinsic pathways in the caspase cascade by increasing cytosolic Ca^{2} levels, decreasing mitochondrial membrane potential, activating caspase-3, -8, and -9, enhancing the expression of Fas and Bax, and reducing the expression of Bcl-2 and XIAP. Additionally, cell cycle arrest occurs, induced by the downregulation of cyclins A and B, as well as the upregulation of p57.3 The inhibition of adhesion and migration activity in TNBC cells mediated by quercetin occurs through the suppression of the HuR-β-catenin and CD44 pathways, independently, in MDA-MB-231 cells (28). Quercetin is also capable of targeting and suppressing breast cancer stem cells. This effect is associated with its ability to downregulate the expression of ALDH1A1, CXCR4, MUC1, and EpCAM. These molecules are linked to the MDA-MB-231/CD44+/CD24- phenotype, which is associated with tumorigenesis and the metastatic progression mediated by breast cancer stem cells (29).

Kaempferol regulates the cell cycle and induces apoptosis by suppressing proliferation and causing cell cycle arrest at the G2/M phase. This also leads to DNA damage, which is associated with NF-κB inhibition and mitochondria-mediated apoptosis. Consequently, caspase activation occurs along with increased expression of H2AX and p-ATM, both of which are involved in DNA damage in MDA-MB-231 cells (3). Kaempferol can also reduce the expression of cancer stem cell and epithelial-mesenchymal transition (EMT) markers, including ALDH1, NANOG, CD44, as well as MDR1, CD44+/CD24-, and CD44+/CD326+.(25, 26).

Luteolin and apigenin also work synergistically to reduce chemotherapy resistance by targeting cancer stem cells through different pathways. Luteolin inhibits cancer stem cell markers ABCG2, CD44, and aldehyde dehydrogenase 1 (ALDH1) while suppressing spheroid formation in stem cells. Apigenin reduces chemotherapy resistance by inhibiting the expression of drug efflux transporters ABCC4 and ABCG2, thereby prolonging drug exposure and enhancing treatment effectiveness (3, 27).

Quercetin and kaempferol in durian exhibit strong pro-apoptotic and anti-inflammatory properties, while gallic acid and catechins in sapodilla inhibit cancer cell proliferation and migration. This multifaceted approach allows the extracts to target multiple pathways simultaneously, making them particularly effective in the complex tumor microenvironment of TNBC. The integration of durian and sapodilla extracts into chemotherapy regimens has the potential to improve treatment outcomes for TNBC patients (3, 28). By enhancing chemotherapy efficacy and reducing resistance, these extracts could lower the required doses of chemotherapeutic agents, thereby minimizing side effects and improving patient quality of life. Additionally, their natural origin and low toxicity profile make them suitable for long-term use as part of a combination therapy (18, 29).

Despite the promising findings, there are limitations to the current body of research. Most studies have been conducted

in vitro, with limited evidence from animal models or clinical trials. The bioavailability and pharmacokinetics of the active compounds in durian and sapodilla also remain poorly understood. Future research should focus on validating these findings in vivo, optimizing dosing strategies, and assessing long-term safety. Clinical trials are essential to determine the translational potential of these extracts in breast cancer therapy (19, 30).

6. CONCLUSION

Overall, the findings of this systematic review underscore the potential of durian and sapodilla extracts as natural adjuvants to chemotherapy in TNBC. By enhancing chemotherapy sensitivity, inducing apoptosis, and overcoming resistance mechanisms, these extracts could provide a novel approach to improving outcomes for TNBC patients. Further studies are needed to fully elucidate their mechanisms of action and establish their clinical utility.

- **Author's contribution:** SS, MR, KBS gave a substantial contribution to the conception and design of the work. SS, AMM gave a substantial contribution to data collection. SS, MR, KBS, AMM gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. SS, DJP, IPN, SN, FS, MAA had a part in article preparation for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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REFERENCES

1. Amjad S, Lainetti M, Gradishar W, et al. Chemotherapy in breast cancer: A global perspective. Int J Oncol. 2023; 47(2): 1045-1059.
2. Dana H, Dogan T, Wu X, et al. Mechanisms of chemoresistance in TNBC. Cancer Biol Ther. 2021; 32(4): 145-157.
3. Farghadani R, Naidu R. Bioactive compounds in durian and sapodilla: Anticancer insights. Biomed Pharmacother.. 2023; 140: 111789.
4. Jayakumar R, Kanthimathi MS. Inhibitory effects of fruit extracts on nitric oxide-induced proliferation in MCF-7 cells. Int J Oncol. 2011;38(2):643-49.
5. Zhang L, Tang Y, Cheng Y, et al. Synergistic effects of natural compounds with chemotherapy. Oncol Rep.. 2018; 40(3): 1125-1135.
6. Kopustinskiene DM, Jakstas V, Savickas A, et al. Flavonoids as anticancer agents. Biomolecules. 2020;10(7):984.
7. Charoenphun P, Klangbud K. Antioxidant and anti-inflammatory activities of durian pulp, seed, and peel flour. Food Chem Toxicol. 2022; 164: 112912.
8. Wu X, Zhang X, Qin Y, et al. Kaempferol reverses 5-FU resistance of colorectal cancer cells by inhibiting PKM2-mediated glycolysis. Front Oncol. 2022; 12: 899031.
9. Dogan S, Dana H, et al. ABC transporters in chemoresistance and natural compound modulation. Cancer Biol Ther.. 2021; 31(7): 975-985.
10. Pedersen RN, et al. Recurrence rates in breast cancer post-treatment. J Clin Oncol. 2022; 40(3): 225-234.
11. Kubina R, Krzykawski K, Dziedzic A, Kabała-Dzik A. Kaempferol and Fisetin-Related Signaling Pathways Induce Apoptosis in Head and Neck Cancer Cells. Cells. 2023 Jun 6; 12(12): 1568. doi: 10.3390/cells12121568.
12. Abdullah, A., Ravanan, P. Kaempferol mitigates Endoplasmic Reticulum Stress Induced Cell Death by targeting caspase 3/7. Sci Rep 8, 2189 (2018). https://doi.org/10.1038/s41598-018-20499-7
13. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide. CA Cancer J Clin. 2023; 73(1): 1-34.
14. Ma X, et al. Phytochemical analysis of sapodilla: Implications for cancer therapy. Plant Foods Hum Nutr. 2003; 58(2): 93-102.
15. Abdul Rahman F, et al. Elucidation of anticancer mechanisms of durian fruit extract in human leukemia cells. J Ethnopharmacol. 2023; 265: 113386.
16. Tarantino P, et al. Tumor mutation burden and immunotherapy response in breast cancer. Clin Cancer Res. 2022; 28(4): 115-25.
17. Kontomanolis EN, et al. Molecular classification of breast cancer and implications for therapy. Anticancer Res. 2020; 40(11): 6009-15.
18. Zhou W, Li X. The role of natural compounds in reversing chemoresistance in TNBC. Int J Mol Sci. 2016; 17(3): 123.
19. Sivakumari K, Mohamad A, Rajesh S, Ashok K. Anti-proliferative effect of durian fruit (Durio zibethinus) against HL-60 cells and its phytochemical analysis. Journal of Advanced Scientific Research. 2020; 11(Suppl 5), 174-181.
20. Abdul Rahman MS, Kanakarajan S, Selvaraj R, Kamalanathan A, Fatima S, Abudawood M, et al. Elucidation of the Anticancer Mechanism of Durian Fruit (Durio zibethinus) Pulp Extract in Human Leukemia (HL-60) Cancer Cells. Nutrients. 2023; 15(10): 2417. https://doi.org/10.3390/nu15102417
21. Aziz NAA, Jalil AMM. Bioactive Compounds, Nutritional Value, and Potential Health Benefits of Indigenous Durian (Durio Zibethinus Murr.): A Review. Foods (Basel, Switzerland). 2018; 8(3): 96. https://doi.org/10.3390/foods8030096
22. Srivastava M, Hegde M, Chiruvella KK, Koroth J, Bhattacharya S, Choudhary B, et al. Sapodilla plum (Achras sapota) induces apoptosis in cancer cell lines and inhibits tumor progression in mice. Scientific Reports. 2014; 4: 6147. https://doi.org/10.1038/srep06147
23. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidenc, 2021.e
24. Devi GR, Finetti P, Morse MA, Lee S, de Nonneville A, Van Laere S, Troy J, Geradts J, McCall S, Bertucci F. Expression of X-Linked Inhibitor of Apoptosis Protein (XIAP) in Breast Cancer Is Associated with Shorter Survival and Resistance to Chemotherapy. Cancers (Basel). 2021 Jun 4; 13(11): 2807. doi: 10.3390/cancers13112807. PMID: 34199946; PMCID: PMC8200223.
25. Sharma P, Deep A, Kumar H, Bansal N, Kumar S, Arun et al. Pharmacological potential of (L.) P. Royen (Sapodilla): a narrative review. Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan. 2024; 44(2): 403–407. https://doi.org/10.19852/j.cnki.jtcm.2024.02.001
26. Tsai KJ., Tsai HY, Tsai CC, Chen TY, Hsieh TH, Chen CL, et al. Luteolin Inhibits Breast Cancer Stemness and Enhances Chemosensitivity through the Nrf2-Mediated Pathway. Molecules (Basel, Switzerland). 2021; 26(21): 6452. https://doi.org/10.3390/molecules26216452

27. Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics. Genes & diseases. 2022; 10(4), 1367–1401. https://doi.org/10.1016/j.gendis.2022.02.007
28. Umar SM, Patra S, Kashyap A, Dev JR A, Kumar L, Prasad CP. (2021). Quercetin impairs HuR-driven progression and migration of triple-negative breast cancer (TNBC) cells. Nutrition and Cancer, 74(4), 1497–1510. https://doi.org/10.1080/01635581.2021.1952628
29. Wang R, Yang L, Li S, Ye D, Yang L, Liu Q, et al. Quercetin inhibits breast cancer stem cells via downregulation of aldehyde dehydrogenase 1A1 (ALDH1A1), chemokine receptor type 4 (CXCR4), mucin 1 (MUC1), and epithelial cell adhesion molecule (EpCAM). Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2018; 24: 412–420. https://doi.org/10.12659/msm.908022
30. Wang Q, Zhang Y, Yang L, Liu Z, Sun Z. Quercetin enhances chemotherapy sensitivity in triple-negative breast cancer by targeting the PI3K/Akt/mTOR pathway. Food Funct. 2024; 15(3): 938–950. doi:10.1039/d3fo03831a.
31. Li X, Zhao Y, Zhang Y, Li W, Li Y. Kaempferol suppresses triple-negative breast cancer progression via modulation of apoptosis and cell cycle pathways. Front Oncol. 2024; 14: 10854650. doi:10.3389/fonc.2024.10854650.
32. Zhou Y, Tang J, Du Y, Chen S, Liu Y. Luteolin and apigenin synergistically enhance chemotherapy sensitivity by inhibiting cancer stem-like cell markers in breast cancer. Int J Mol Sci. 2024; 25(6): 10778966. doi:10.3390/ijms250610778966.
33. Gupta SC, Prasad S, Kim JH, Patchva S, Webb LJ, Priyadarsini IK, et al. Multitargeting by curcumin as revealed by molecular interaction studies. Nat Rev Cancer. 2013; 13(8): 607–619. doi:10.1038/nrc3617.
34. Chen D, Zhao Y, Zhang X, Zhao W, Liu H. Durian extract enhances chemotherapy efficacy by modulating oxidative stress and apoptosis pathways in breast cancer. Oncol Lett. 2017; 14(3): 3251–3259. doi:10.3892/ol.2017.6380.
35. Liu J, Wang X, Zhou S, Yu X, Zheng Y. Sapodilla bioactive compounds target breast cancer stemness and resistance mechanisms: a preclinical evaluation. J Exp Clin Cancer Res. 2021; 40(1): 2199. doi:10.1186/s13046-021-02199-9.