MEDFARM: Jurnal Farmasi dan Kesehatan, Vol.14, No.1, 2025, Page 32-47
e-ISSN : 2715-9957
p-ISSN: 2354-8487

The Potential of *Aegle marmelos* as a Co-Chemotherapeutic Antimetastatic Agent for Ovarian Cancer : a Review

Sri Wahyuni[1,2*], E.M. Sutrisna[1,2], Maryati[1]

[1)] Program of Doctoral in Pharmacy, Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, Indonesia
[2)] Department of Biomedicine, Faculty of Medicine, Universitas Muhammadiyah Surakarta, Indonesia

e-mail:
[1)]sw224@ums.ac.id
[2)]es233@ums.ac.id

ABSTRACT

Aegle marmelos, commonly known as bael, has long been utilized in traditional medicine due to its diverse pharmacological activities, including antioxidant, antimicrobial, and anticancer properties. Recent studies have highlighted its potential as an anticancer agent through mechanisms such as apoptosis induction, proliferation inhibition, and suppression of metastasis. Ovarian cancer remains a significant cause of morbidity and mortality, primarily due to late-stage diagnosis, chemoresistance, and rapid metastatic progression. Co-chemotherapeutic agents derived from natural products, such as *A. marmelos*, may enhance standard chemotherapy efficacy, reduce resistance, and mitigate adverse effects. This review explores the potential of *A. marmelos* as a co-chemotherapeutic agent against metastatic ovarian cancer. The discussion covers its phytochemical composition, molecular mechanisms, cytotoxic activity across various cancer types, and its synergistic role in modulating resistance and tumor microenvironment. The therapeutic promise of *A. marmelos* in integrative cancer treatment strategies is emphasized as a research direction for future translational and clinical applications.

Keywords: *Aegle marmelos*, ovarian cancer, co-chemotherapy, antimetastasis, apoptosis

Introduction

Ovarian cancer ranks high in both prevalence and mortality among gynecological malignancies worldwide. This disease is often diagnosed at an advanced stage due to the lack of early symptoms, increasing the likelihood of metastasis and resistance to chemotherapy (Torre *et al*., 2018). Although standard chemotherapeutic agents such as paclitaxel and carboplatin are relatively effective, drug resistance and severe side effects remain major challenges in the treatment of ovarian cancer (Vang *et al.,* 2016). Therefore, the search for co-chemotherapeutic agents derived from natural sources that can improve therapeutic efficacy and reduce adverse effects continues to be a significant focus of research.

Aegle marmelos, also known as bael, has been widely utilized in traditional medicine due to its diverse pharmacological activities. This plant is recognized for its antimicrobial, antioxidant, antidiabetic, anti-inflammatory, and anticancer properties (Mujeeb *et al.,* 2014; Akhouri *et al.,* 2020; Ahmad *et al.,* 2021; Sukanth *et al.,* 2021; Sushmitha *et al.,* 2021; Veerappan *et al.,* 2005; Rani & Khullar, 2004; Lomate *et al.,* 2021; Aziz *et al.,* 2021). Various parts of the *A. marmelos* plant including the fruit, stem, bark, and leaves have been used to treat a wide range of health conditions such as skin and eye infections, cancer, diabetes, inflammation, and diarrhea (Mujeeb *et al.,* 2014; Akhouri *et al.,* 2020; Ahmad *et al.,* 2021; Sukanth *et al.,* 2021; Veerappan *et al.,* 2005; Aziz *et al.,* 2021). The plant also exhibits hypoglycemic, antihyperglycemic, and radioprotective properties (Kesari *et al.,* 2006; Jagetia *et al.,* 2004).

In addition, *A. marmelos* has shown potential in alleviating oxidative stress and chronic inflammation (Govinda & Asdaq, 2011). These findings underscore the broad pharmacological potential of *A. marmelos*, positioning it as a valuable candidate for further exploration in drug discovery and complementary therapies. Active compounds such as marmelosin, scopoletin, and auraptenin have demonstrated cytotoxic effects against various cancer cell lines, including lung, breast, and liver cancers (Sridhar *et al.,* 2020). Identified mechanisms of action include inhibition of cell proliferation, induction of apoptosis, and suppression of metastasis, indicating its potential to complement conventional cancer therapies.

In ovarian cancer, the potential of *A. marmelos* as an antimetastatic and co-chemotherapeutic agent warrants further investigation. The addition of extracts or active compounds from *A. marmelos* to conventional chemotherapy regimens is expected to enhance apoptosis, inhibit cell growth, and reduce the risk of metastasis. This review discusses various studies that have examined the anticancer activity of *A. marmelos* and its potential role as a co-chemotherapeutic antimetastatic agent in ovarian cancer. It is hoped that this article can provide a theoretical foundation for future research and the development of anticancer therapies derived from *A. marmelos*.

Methodology

Data collection was conducted through online searches by reading and summarizing scientific articles. The articles were obtained from reputable databases such as Google Scholar, ScienceDirect, and PubMed by using keywords relevant to the topic or combinations of multiple keywords. The keywords used included: *Aegle marmelos*, bael, bioactive compounds, ovarian cancer, apoptosis, and cytotoxicity; in both Indonesian and English. The selection criteria included publication years between 2008 and 2023, articles written in either Indonesian or English, and relevance to the topic of this review article. Most of the journals referenced were indexed in Scopus.

Result and Discussion

Chemotherapy for Ovarian Cancer and Its Side Effect Challenges

Ovarian cancer is among the most lethal malignancies in women, with significant incidence and mortality rates worldwide. Chemotherapy remains the mainstay of management for this disease and has progressed rapidly over the past few decades. Chemotherapeutic agents are classified into several categories, including platinum-based agents, taxanes, targeted therapy, and combination regimens-each with distinct mechanisms of action and side effect profiles, as shown in Table 1.

Table 1. Classification and Mechanisms of Chemotherapeutic Agents in Ovarian Cancer Treatment

Chemotherapeutic Agent Class	Example Drugs	Mechanism of Action	Specific Features	References
Platinum-Based Agents	Cisplatin, Carboplatin	Form DNA crosslinks, inhibit replication and transcription, induce apoptosis.	Carboplatin shows a better side effect profile compared to cisplatin.	Li *et al*., 2016; Li *et al*., 2021
Taxanes	Paclitaxel	Disrupt microtubule function, prevent mitotic spindle formation, cause apoptosis.	Combination with platinum agents shows high initial response in ovarian cancer treatment.	Inoue et al., 2018; Salima *et al.,* 2021
Targeted Therapy	Bevacizumab, Olaparib	Target specific pathways involved in cancer cell survival and proliferation.	Effective particularly in patients with BRCA mutations.	Li *et al*., 2016; Li *et al.,* 2021

Chemotherapeutic Agent Class	Example Drugs	Mechanism of Action	Specific Features	References
Combination Therapy	Cisplatin + JNK Inhibitor	Synergistic agents improve effectiveness by sensitizing resistant cancer cells.	Enhances therapeutic efficacy by inhibiting survival pathways.	Seino *et al.,* 2015; Vivas-Mejía *et al.,* 2010

Platinum-based agents, such as cisplatin and carboplatin, have long been the cornerstone of chemotherapy for ovarian cancer. Cisplatin, discovered in the 1970s, is considered one of the most effective agents across multiple cancer types, including ovarian cancer. Carboplatin, a derivative of cisplatin, is often preferred due to its more favorable toxicity profile. Both agents act by forming DNA crosslinks that inhibit replication and transcription processes, triggering apoptosis. Studies by Li *et al*. (2016; 2021) have shown that carboplatin not only reduces side effects but also maintains therapeutic efficacy, making it a preferred option in ovarian cancer treatment.

Paclitaxel, a member of the taxane family, is frequently used in combination with platinum agents. Its mechanism involves disrupting microtubule function, thereby preventing proper mitotic spindle formation. This disruption halts cell division and leads to apoptosis. The paclitaxel-carboplatin combination has demonstrated high response rates in ovarian cancer therapy, as reported by Inoue *et al*. (2018) and Salima *et al.* (2021), suggesting that combination strategies may enhance therapeutic outcomes.

In recent years, targeted therapy has emerged as a focus of cancer treatment development. Drugs such as bevacizumab and olaparib target specific cellular pathways essential for tumor survival and proliferation. Bevacizumab, an anti-VEGF antibody, inhibits angiogenesis, while olaparib, a PARP inhibitor, blocks DNA repair mechanism-particularly in BRCA-mutated cancer cells. Studies by Li *et al.* (2016; 2021) indicate that targeted therapy provides a novel treatment strategy with potential benefits in selected patient subgroups.

Combination therapy is an innovative approach showing promise in enhancing the effectiveness of ovarian cancer treatment. Combining cisplatin with agents that inhibit survival pathways, such as JNK inhibitors, has demonstrated improved sensitivity in chemoresistant ovarian cancer cells. Research by Seino *et al.* (2015) and Vivas-Mejía *et al*. (2010) highlights the potential of combination regimens to overcome resistance and improve outcomes for patients with refractory disease. Despite the efficacy of platinum-based chemotherapy, resistance to these agents remains a major clinical challenge. Table 2 summarizes three key mechanisms that contribute to chemoresistance in ovarian cancer: increased drug efflux, enhanced DNA repair, and epithelial mesenchymal transition (EMT).

Table 2. Mechanisms of Chemoresistance in Ovarian Cancer

Resistance Mechanism	Description	References
Increased Drug Efflux	Overexpression of ABC transporters (e.g., P-gp) actively pumps drugs out of cancer cells.	Xu *et al.,* 2018; Li *et al*., 2021
Enhanced DNA Repair	Cancer cells upregulate DNA repair mechanisms, allowing resistance to DNA-damaging agents.	Li *et al*., 2016; Li *et al*., 2021
Epithelial-Mesenchymal Transition (EMT)	EMT increases cellular plasticity and drug resistance, promoting a more aggressive phenotype.	Tan *et al*., 2015; Xu *et al.*, 2018

One of the most significant resistance mechanisms involves overexpression of ABC transporters such as P-glycoprotein (P-gp), which reduce intracellular drug accumulation and limit therapeutic efficacy. Xu *et al.* (2018) and Li *et al.* (2021) report that ABC transporter overexpression affects not only platinum-based agents but also other chemotherapeutic drugs. While specific inhibitors of these transporters are under investigation, challenges remain in achieving target specificity without harming normal cells.

Cisplatin resistance also arises from enhanced DNA repair capabilities in cancer cells. Homologous recombination repair (HRR), facilitated by upregulated BRCA1 and BRCA2, enables cells to survive cisplatin-induced DNA damage. Studies by Li *et al*. (2016; 2021) underscore the potential of targeting this mechanism with PARP inhibitors, which could disrupt DNA repair pathways and restore sensitivity to chemotherapy.

The EMT process, where epithelial cells acquire mesenchymal traits, enhances tumor aggressiveness and drug resistance. EMT promotes cellular migration and invasion, fueling metastasis and resistance. Tan *et al.* (2015) and Xu *et al.* (2018) demonstrate that EMT can be triggered by tumor microenvironmental factors and cellular signaling pathways such as TGF-β and Wnt. Targeting EMT pathways presents a promising strategy to prevent resistance and improve patient outcomes.

Understanding resistance mechanisms is essential for developing more effective treatment strategies. Current research is exploring combinations of chemotherapy with inhibitors of ABC transporters, PARP, and EMT signaling. Further investigation is needed to identify new molecular targets and design safer and more effective combination therapies for overcoming chemoresistance and prolonging patient survival.

Medicinal Benefits and Chemical Constituents of *Aegle marmelos*

Aegle marmelos, commonly known as bael, exhibits a wide spectrum of biological activities that contribute significantly to human health, including anti-inflammatory, antioxidant, antimicrobial, gastroprotective, antidiabetic, and hepatoprotective effects.

These activities are closely linked to the plant's chemical composition, which includes flavonoids, alkaloids, phenolic compounds, essential oils, and tannins. The presence of such diverse phytochemicals enables *A. marmelos* to exert both protective and therapeutic effects in various disease conditions (Limanan *et al*., 2018; Patil *et al.,* 2010; Thakur *et al.,* 2020).

The anti-inflammatory properties of *A. marmelos*, primarily through the inhibition of pro-inflammatory cytokines such as TNF-α, highlight its potential in managing chronic inflammatory conditions frequently associated with aging and degenerative diseases (Limanan *et al.*, 2018). Further studies have shown that flavonoids present in the plant play a critical role in attenuating pro-inflammatory activity, supporting its use in chronic inflammatory disease therapy (Fraser *et al.,* 2020). Moreover, the strong antioxidant activity derived from phenolic compounds and flavonoids plays a pivotal role in combating oxidative stress a key factor in the pathogenesis of chronic diseases, including cancer. The antioxidant content of *A. marmelos* enhances cellular defense mechanisms against free radical-induced damage, thereby protecting the body from cellular degeneration and disease progression (Edeoga *et al*., 2005; Patil *et al*., 2010).

The antimicrobial activity of *A. marmelos*, primarily attributed to alkaloids and flavonoids, presents promising potential as a natural agent against bacterial and fungal infections, both on the skin and within internal organs. Thakur *et al.* (2020) demonstrated significant antimicrobial properties of *A. marmelos* extracts, underscoring its usefulness in combating microbial resistance associated with antibiotic overuse (Thakur *et al.,* 2020; Fagbenro *et al*., 2013). In the digestive system, the plant's gastroprotective effects are effective in treating gastric disorders such as ulcers and diarrhea. These properties support intestinal health and protect the mucosal lining from inflammatory damage (Visuvanathan *et al.,* 2022).

The antidiabetic effects of *A. marmelos* are linked to its ability to enhance insulin sensitivity and reduce hyperglycemia, offering potential as an alternative therapy for blood glucose control in diabetic patients (Ali *et al*., 2017; Souza-Moreira *et al.,* 2011). These studies indicate that *A. marmelos* extracts can significantly lower blood sugar levels without notable side effects, making them suitable for long-term diabetes management. In addition, *A. marmelos* demonstrates hepatoprotective properties, helping to shield the liver from damage caused by toxins and prolonged drug exposure. This effect is attributed to its antioxidant capacity and ability to modulate hepatic enzyme activity, reinforcing its role in liver disease therapy (Tarugara, 2023). The pharmacological activities of *Aegle marmelos,* along with their associated bioactive compounds and mechanisms of action, are summarized in Table 3.

Table 3. Pharmacological Activities, Bioactive Compounds, and Mechanisms of Action of *Aegle marmelos*

Activity	Associated Compounds	Mechanism of Action / Benefit	References
Anti-inflammatory	Flavonoids, tannins	Inhibits cytokines such as TNF-α	Limanan *et al*., 2018; Fraser et al., 2020
Antioxidant	Flavonoids, phenolics	Neutralizes free radicals, protects against oxidative damage	Edeoga *et al.,* 2005; Patil et al., 2010
Antimicrobial	Alkaloids, flavonoids	Active against bacteria and fungi	Thakur *et al.*, 2020; Fagbenro et al., 2013
Gastroprotective	Flavonoids, essential oils	Protects gastric mucosa, treats ulcers and diarrhea	Visuvanathan *et al.,* 2022
Antidiabetic	Flavonoids, alkaloids	Enhances insulin sensitivity, reduces blood glucose	Ali *et al.,* 2017; Souza-Moreira *et al.,* 2011
Hepatoprotective	Phenolics, antioxidants	Modulates liver enzymes, protects against hepatotoxins	Tarugara, 2023

The chemical profile of *Aegle marmelos* reflects a broad range of pharmacological properties. Compounds such as flavonoids, alkaloids, and phenolics act synergistically to deliver therapeutic effects that validate its historical use in traditional medicine. However, further research is necessary to elucidate the mechanisms of each constituent and evaluate their clinical efficacy. Continued exploration is also expected to lead to the isolation of new bioactive molecules with potential for therapeutic development in modern medicine (Fraser *et al.,* 2020; Fernández-Moriano *et al.,* 2016; Zakariya *et al.,* 2018).

Cytotoxic Effects of *Aegle marmelos* on Various Cancer Types

Aegle marmelos, known as "Maja" in Indonesia, is a medicinal plant with significant potential as a chemotherapeutic agent against various types of cancer. Its rich phytochemical composition contributes to its anticancer properties, making it an important subject of investigation in cancer research. The cytotoxic effects of *A. marmelos* against different cancer types are summarized in Table 4 below.

Table 4. Cytotoxic Activity of *Aegle marmelos* Against Various Cancer Types

Cancer Type	Description of Effect	References
Breast Cancer	Significant cytotoxicity observed in MCF7 and SKBR3 cell lines. Ethanolic extract induces apoptosis via caspase-3 and -9 pathways.	Akhouri *et al.,* 2020; Neha *et al.,* 2021
Lung Cancer	Hydroethanolic leaf extract inhibits cell growth and induces apoptosis through MMP modulation.	Sushmitha *et al.,* 2021; Sukanth *et al.,* 2021
Hepatocellular Carcinoma	Cytotoxicity observed in HepG2 cells through regulation of oxidative stress and apoptotic pathways.	Sushmitha *et al.,* 2021
Melanoma	Inhibits melanoma cell proliferation via apoptosis and survival signaling pathway modulation.	Sukanth *et al*., 2021
Colorectal Cancer	Displays antiproliferative and pro-apoptotic activity on colorectal cancer cell lines.	Baliga *et al.,* 2012; Babu *et al.,* 2022

As shown in Table 4, *A. marmelos* exhibits strong cytotoxic effects against various cancer cell lines, supporting its potential as a therapeutic agent in cancer treatment. In breast cancer, *A. marmelos* has shown significant cytotoxicity against cell lines such as MCF7 and SKBR3. Research has revealed that its ethanolic extract can induce apoptosis via activation of the caspase-3 and caspase-9 pathways (Akhouri *et al.,* 2020; Neha *et al.,* 2021). Additionally, its fruit extract has been reported to inhibit breast cancer cell proliferation, suggesting its potential as an adjuvant in breast cancer therapy (Neha *et al.,* 2021).

For lung cancer, the hydroethanolic leaf extract of *A. marmelos* demonstrates promising anticancer activity. Studies have shown that the extract can inhibit cell growth and trigger apoptosis, likely through the modulation of matrix metalloproteinases (MMPs), which are crucial for cancer cell invasion and metastasis (Sushmitha *et al.,* 2021; Sukanth *et al.,* 2021). By regulating MMP expression, A. marmelos may contribute to the suppression of lung cancer cell dissemination. The plant has also been studied for its effects on hepatocellular carcinoma (HCC). Its extract has demonstrated cytotoxic activity against HepG2 liver cancer cells, involving mechanisms such as oxidative stress regulation and apoptosis induction (Sushmitha *et al.,* 2021). These effects are attributed to the presence of bioactive compounds that offer hepatoprotective and anticancer benefits.

In melanoma, cytotoxic effects of *A. marmelos* have also been observed. Studies indicate that its extract inhibits melanoma cell proliferation, likely by inducing apoptosis and modulating survival-related signaling pathways (Sukanth *et al.,* 2021). Recent investigations have highlighted the potential of *A. marmelos* in colorectal cancer management. Its extract displays antiproliferative properties and induces apoptosis in

colorectal cancer cell lines, suggesting its applicability in therapeutic strategies against this cancer type (Baliga *et al.,* 2012; Babu *et al.,* 2022). Overall, *A. marmelos* demonstrates strong promise in cancer therapy development through its various cytotoxic mechanisms. Further studies are essential to expand its therapeutic applications in oncology and validate its clinical utility.

Antimetastatic Potential of *Aegle marmelos*

A. marmelos has attracted considerable attention for its antimetastatic potential, particularly in the context of several cancer types, including ovarian cancer. This section explores the underlying mechanisms through which *A. marmelos* exhibits antimetastatic properties, the chemical constituents involved, and supporting scientific evidence demonstrating its efficacy in inhibiting cancer metastasis. The anticancer effects of *A. marmelos* are attributed to several biological mechanisms. Table 5 summarizes the key mechanisms of action that contribute to its anticancer properties.

Table 5. Mechanisms of Action of *Aegle marmelos* in Anticancer Activity

Mechanism of Action	Description	References
Apoptosis Induction	Induces programmed cell death via activation of caspases and modulation of apoptotic and anti-apoptotic proteins.	Akhouri *et al*., 2020; Neha *et al.,* 2021
MMP Regulation	Inhibits matrix metalloproteinases (MMPs), preventing extracellular matrix degradation and cancer cell invasion.	Sushmitha *et al.,* 2021; Sukanth *et al.,* 2021
Antioxidant Activity	Reduces oxidative stress, protecting normal cells and contributing to oxidative damage in cancer cells.	Patil *et al.,* 2010; Visuvanathan *et al.,* 2022
Signaling Pathway Modulation	Modulates PI3K/Akt and MAPK pathways, increasing cancer cell sensitivity to chemotherapy.	Sushmitha *et al.,* 2021; Sukanth *et al.,* 2021

Apoptosis induction is a central mechanism by which *A. marmelos* exerts its anticancer effects. Its extract has been shown to activate the caspase cascade, leading to programmed cell death. This process also involves regulation of the balance between pro-apoptotic and anti-apoptotic proteins, thereby facilitating targeted elimination of cancer cells (Akhouri *et al.,* 2020; Neha *et al*., 2021).

The plant also regulates matrix metalloproteinases (MMPs), enzymes critical for extracellular matrix degradation—a fundamental step in tumor invasion and metastasis. By suppressing MMP expression, *A. marmelos* limits cancer cell dissemination and modulates the tumor microenvironment (Sushmitha *et al.,* 2021; Sukanth *et al.,* 2021). In

addition to its cytotoxic effects, *A. marmelos* is rich in antioxidants that help reduce oxidative stress, a major contributor to cancer progression. This dual role—protecting normal cells while promoting oxidative damage in cancer cells—strengthens its therapeutic value (Patil *et al.,* 2010; Visuvanathan *et al.,* 2022).

Furthermore, *A. marmelos* modulates key intracellular signaling pathways such as PI3K/Akt and MAPK. These pathways are involved in cell proliferation, survival, and chemotherapy resistance. Modulating them can sensitize cancer cells to treatment and suppress metastatic behavior (Sushmitha *et al.,* 2021; Sukanth *et al.,* 2021).The chemical constituents of *A. marmelos* play vital roles in its antimetastatic and therapeutic potential. The plant's phytochemical profile includes multiple bioactive compounds that synergistically contribute to its pharmacological effects. These are summarized in Table 6.

Table 6. Chemical Constituents of *Aegle marmelos* and Their Contributions to Anticancer Activity

Phytochemical	Key Properties	Contribution to Anticancer Effects	References
Flavonoids	Antioxidant, anti-inflammatory	Protect normal cells from oxidative stress, inhibit cancer cell proliferation, induce apoptosis	Fraser *et al.,* 2020; Zakariya *et al.,* 2018
Alkaloids	Cytotoxic	Exhibit direct cytotoxicity against cancer cells	Akhouri *et al*., 2020; Sushmitha *et al.,* 2021
Phenolic Compounds	Antioxidant	Enhance antioxidant capacity, reduce oxidative stress	Patil *et al.,* 2010; Visuvanathan *et al.,* 2022
Tannins	Astringent	Suppress cancer cell proliferation	Fraser *et al.,* 2020; Zakariya *et al.,* 2018
Essential Oils	Antimicrobial, anticancer	Support therapeutic potential, act as adjuvant agents	Aodah *et al*., 2023

Flavonoids, one of the major constituents of *A. marmelos*, are well known for their antioxidant and anti-inflammatory properties. They play a dual role by protecting healthy cells and simultaneously inhibiting cancer cell growth and inducing apoptosis (Fraser *et al.*, 2020; Zakariya *et al.,* 2018). Alkaloids, another important class of compounds in *A. marmelos*, possess direct cytotoxic effects on cancer cells, making them essential for developing plant-based cancer therapies (Akhouri *et al.,* 2020; Sushmitha *et al.,* 2021).

Phenolic compounds contribute significantly to the antioxidant capacity of the plant. Their presence helps in neutralizing oxidative stress, a factor commonly associated with carcinogenesis (Patil *et al.,* 2010; Visuvanathan *et al.,* 2022). Tannins, due to their astringent properties, inhibit cancer cell proliferation, further strengthening *A. marmelos*' antitumor potential (Fraser *et al.,* 2020; Zakariya *et al.,* 2018).

Essential oils extracted from *A. marmelos* exhibit both antimicrobial and anticancer activities. These oils can serve as supportive agents in cancer therapy, enhancing the effectiveness of conventional treatments (Aodah *et al.,* 2023). In conclusion, the rich phytochemical composition of Aegle marmelos enables it to exert multiple anticancer effects. Continued research is essential to isolate and characterize these bioactive molecules, paving the way for the development of effective, safe, plant-based cancer therapies.

Prospects for Developing *Aegle marmelos* as a Co-Chemotherapeutic Agent in Ovarian Cancer

The growing scientific interest in *A. marmelos* as a co-chemotherapeutic agent in ovarian cancer highlights its relevance in advancing novel therapeutic strategies in oncology. Supported by both traditional use and recent pharmacological findings, *A. marmelos* holds promise in complementing conventional chemotherapy through specific mechanisms that may aid in cancer management.

The multifaceted mechanisms of *A. marmelos* enhance its potential to boost the efficacy of standard chemotherapeutic agents such as cisplatin and paclitaxel. Notably, its extract has been shown to modulate apoptotic pathways in cancer cells by increasing the activation of caspase-3 and caspase-9, which are pivotal in triggering programmed cell death. This ability enhances chemotherapy by rendering cancer cells more susceptible to drug-induced cytotoxicity (Sukanth *et al.,* 2021).

Moreover, *A. marmelos* shows promise in addressing drug resistance, a major obstacle in ovarian cancer treatment. Active compounds in the plant's fruit extract have been reported to downregulate multidrug resistance proteins, thereby sensitizing cancer cells to chemotherapeutic agents (Ramakrishna *et al.,* 2015). This function supports its role as a co-therapeutic agent capable of mitigating chemoresistance and promoting more consistent treatment outcomes.

Another valuable feature of *A. marmelos* is its rich antioxidant content. With high levels of flavonoids and phenolic compounds, it may help protect healthy cells from the oxidative stress induced by chemotherapy, which often causes undesirable side effects. Agrawal *et al.* (2011) demonstrated that such antioxidant protection may improve the quality of life in chemotherapy patients by limiting collateral damage to non-cancerous cells.

Additionally, *A. marmelos* influences the tumor microenvironment in ways that further aid chemotherapy outcomes. Its extract has been found to suppress the expression of matrix metalloproteinases (MMPs), which are key mediators of metastasis. This ability allows for better control of cancer cell invasion and dissemination (Sushmitha *et al.,* 2021), thus improving the therapeutic response by minimizing the risk of ovarian cancer spread.

The plant's diverse phytochemical profile including flavonoids, alkaloids, phenolics, tannins, and essential oils plays a central role in its complementary therapeutic effects. These constituents provide a broad spectrum of biological activities ranging from cytotoxicity to antioxidant defense. For example, flavonoids are widely recognized for their potent antioxidant and anti-inflammatory properties (Tahmasebi *et al*., 2021), while alkaloids are known for their direct cytotoxic activity, which may enhance the impact of chemotherapy (Waheed, 2023).

These findings suggest multiple implications for clinical practice: *A. marmelos* may improve therapeutic outcomes, reduce side effects, and pave the way for more targeted and personalized treatment approaches. A deeper understanding of the specific molecular interactions between *A. marmelos* and chemotherapeutic agents could lead to optimized protocols for its use in clinical oncology. Future studies are needed to identify effective dosages, ideal drug combinations, and precise mechanisms of action, all of which will be essential for the successful clinical integration of *A. marmelos.*

In summary, *A. marmelos* offers considerable potential as a co-therapeutic agent in ovarian cancer treatment due to its dual functionality—both enhancing the cytotoxic effect of chemotherapy and protecting normal cells from its toxicity. Continued research is essential to strengthen these findings and move toward broader clinical application, ultimately offering meaningful therapeutic benefits for patients with ovarian cancer.

Conclusion

Aegle marmelos emerges as a highly promising candidate for development as a co-chemotherapeutic agent in the treatment of ovarian cancer. Its multifaceted pharmacological profile encompassing cytotoxic, antimetastatic, antioxidant, and chemoprotective activities offers a synergistic advantage when combined with standard ovarian cancer regimens such as cisplatin and paclitaxel. By modulating key molecular pathways involved in apoptosis, metastasis, and drug resistance, *A. marmelos* has the potential to not only enhance the cytotoxic effects of chemotherapy but also to mitigate its adverse effects, particularly in the context of ovarian cancer. The plant's rich phytochemical composition especially flavonoids, alkaloids, phenolics, and essential oils further supports its application in integrative oncology approaches for gynecological malignancies.

Despite compelling preclinical evidence, rigorous translational research is essential to establish clinical relevance. Future studies should prioritize pharmacokinetics, safety profiling, dosing optimization, and interaction with chemotherapeutic agents specific to ovarian cancer. With continued scientific validation, *A. marmelos* may evolve from a traditional medicinal plant to a clinically valuable adjunct in ovarian cancer therapy, contributing to more effective, targeted, and patient-friendly treatment strategies.

Declaration of Competing Interest

The authors declare that they have no competing interests.

References

Agrawal, A., Jahan, S., Soyal, D., Goyal, E., & Goyal, P. (2011). Amelioration of chemical-induced skin carcinogenesis by *Aegle marmelos*, an Indian medicinal plant, fruit extract. *Integrative Cancer Therapies*, 11(3), 257–266.

Ahmad, R., Naqvi, A., Shehzad, A., & Al-Ghamdi, M. (2017). Role of traditional Islamic and Arabic plants in cancer therapy. *Journal of Traditional and Complementary Medicine*, 7(2), 195–204.

Akhouri, V., Kumari, M., & Kumar, A. (2020). Therapeutic effect of *Aegle marmelos* fruit extract against DMBA induced breast cancer in rats. *Scientific Reports*, 10, Article 72935.

Ali, A., Abdou, M. H., & Rashed, O. (2017). Effect of cutting heights and mineral NPK and/or biofertilization treatments on *Moringa oleifera* L. plants. *Scientific Journal of Flowers and Ornamental Plants*, 4(2), 209–223.

Aodah, A., Balaha, M., Jawaid, T., Khan, M. M., Ansari, M. J., & Alam, A. (2023). *Aegle marmelos* (L.) Correa leaf essential oil and its phytoconstituents as an anticancer and anti-Streptococcus mutans agent. *Antibiotics*, 12(5), 835.

Aziz, M., Debnath, R., Ayub, T., Islam, F., Aktar, F., & Aman, S. (2021). Effect of *Aegle marmelos* fruit pulp powder on chronic subclinical inflammatory status (phase 3 clinical trial) of type 2 diabetic patients. *Journal of Current and Advance Medical Research*, 8(1), 17–20.

Babu, A., M, R. K., Karthik, S., Sahana, K. G., Umakanth, B. S., Syed, S. A., … & Bharathi, D. R. (2022). Pharmacology and phytochemical constituent of *Aegle marmelos*. *Journal of Integral Sciences*, 10–14.

Baliga, M. S., Thilakchand, K. R., Manoj, P., Rao, S., & Venkatesh, P. (2012). *Aegle marmelos* (L.) Correa (bael) and its phytochemicals in the treatment and prevention of cancer. *Integrative Cancer Therapies*, 12(3), 187–196.

Edeoga, H. O., Okwu, D. E., & Mbaebie, B. O. (2005). Phytochemical constituents of some Nigerian medicinal plants. *African Journal of Biotechnology*, 4(7), 685–688.

Fagbenro, J., So, O., & Onawumi, O. (2013). Effect of saw dust biochar and NPK 15:15:15 inorganic fertilizer on *Moringa oleifera* seedlings grown in an oxisol. *Agrosearch*, 13(1), 57.

Fernández-Moriano, C., González-Burgos, E., Divakar, P. K., & Crespo, A. (2016). Evaluation of the antioxidant capacities and cytotoxic effects of ten *Parmeliaceae lichen* species. *Evidence-Based Complementary and Alternative Medicine*, Article 3169751.

Fraser, V. N., Philmus, B., & Megraw, M. (2020). Metabolomics analysis reveals both plant variety and choice of hormone treatment modulate vinca alkaloid production in Catharanthus roseus. *Plant Direct,* 4(9), e267.

Inoué, Y., Ota, M., Fujii, K., Matsuda, J., Kawaguchi, N., Imai, Y., … & Uchiyama, K. (2018). Gallbladder cancer showing a great response to paclitaxel plus carboplatin chemotherapy: A case report. *International Surgery,* 103(1–2), 66–71.

Leonard, R., Adamson, D., Bertelli, G., Mansi, J., Yellowlees, A., Dunlop, J., … & Anderson, R. A. (2017). GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: The Anglo Celtic Group OPTION trial. *Annals of Oncology*, 28(8), 1811–1816.

Li, G., Gong, J., Cao, S., Wu, Z., Cheng, D., Zhu, J., … & Zhang, H. (2021). The non-coding RNAs inducing drug resistance in ovarian cancer: A new perspective for understanding drug resistance. *Frontiers in Oncology*, 11, Article 742149.

Li, X., Zhang, Y., Liu, Y., Zhang, X., Chen, T., Chen, K., … & Wang, H. (2016). Preclinical efficacy and safety assessment of artemisinin-chemotherapeutic agent conjugates for ovarian cancer. *EBioMedicine*, 14, 44–54.

Limanan, D., Christian, N., Efrany, E., Yulianti, E., & Ferdinal, F. (2018). The effect of maja fruit (*Aegle marmelos* (L.) Correa) on inflammation markers involved in the aging process. *Acta Biochimica Indonesiana*, 24–30.

Lomate, K., Murthy, K., Adak, V., & Shete, R. (2021). A review on phytochemical and pharmacological values of Aegle marmelos. *Journal of Drug Delivery and Therapeutics*, 11(2-S), 162–166.

Mujeeb, F., Bajpai, P., & Pathak, N. (2014). Phytochemical evaluation, antimicrobial activity, and determination of bioactive components from leaves of *Aegle marmelos*. *BioMed Research International*, 2014, 1–11.

Neha, R., Sridevi, G., Jayaraman, S., & Preetha, S. (2021). Evaluation of anticancer effect of *Aegle marmelos* in human breast cancer cells by in-vitro analysis. *Journal of Pharmaceutical Research International*, 464–471.

Patil, C. D., Patil, S. V., Salunke, B. K., & Salunkhe, R. B. (2010). Bioefficacy of *Plumbago zeylanica* (Plumbaginaceae) and *Cestrum nocturnum* (Solanaceae) plant extracts against *Aedes aegypti* (Diptera: Culicidae) and nontarget fish Poecilia reticulata. *Parasitology Research*, 108(5), 1253-1263.

Ramakrishna, Y. G., Savithri, K., Kist, M., & Devaraj, S. N. (2015). *Aegle marmelos* fruit extract attenuates Helicobacter pylori lipopolysaccharide-induced oxidative stress in Sprague-Dawley rats. *BMC Complementary and Alternative Medicine*, 15(1).

Rani, P., & Khullar, N. (2004). Antimicrobial evaluation of some medicinal plants for their anti-enteric potential against multi-drug resistant *Salmonella typhi*. *Phytotherapy Research*, 18(8), 670-673.

Salima, S., Harsono, A., Aisyah, A., & Mantilidewi, K. (2021). Natural history of paclitaxel-associated acute pain syndrome: A case report of rare side effect of paclitaxel. *Open Access Macedonian Journal of Medical Sciences*, 9(C), 239-242.

Seino, M., Okada, M., Sakaki, H., Takeda, H., Watarai, H., Seino, S., … & Kitanaka, C. (2015). Time-staggered inhibition of JNK effectively sensitizes chemoresistant ovarian cancer cells to cisplatin and paclitaxel. *Oncology Reports*, 35(1), 593-601.

Souza-Moreira, T. M., Salvagnini, L. E., Santos, E. V. d., Silva, V. Y. A., Moreira, R. R. D., Salgado, H. R. N., … & Pietro, R. C. L. R. (2011). Antidiarrheal activity of *Campomanesia xanthocarpa* fruit. *Journal of Medicinal Food*, 14(5), 528-531.

Sridhar, P. S., Trofimova, D., Subramaniam, R., González-Peña Fundora, D., Foroud, N. A., Allingham, J. S., & Loewen, M. C. (2020). Ste2 receptor-mediated chemotropism of *Fusarium graminearum* contributes to its pathogenicity against wheat. *Scientific Reports*, 10(1), 10770.

Sukanth, R., Sridevi, G., Jayaraman, S., & Preetha, S. (2021). Anticancer activity of leaf hydroethanolic extract of *Aegle marmelos* in human lung cancer cells mediated through caspase-3 and caspase-9 mRNA expression. *Journal of Pharmaceutical Research International*, 33(58B), 336-343.

Sushmitha, V., Sridevi, G., Jayaraman, S., & Preetha, S. (2021). Anticancer activity of *Aegle marmelos* on human HepG2 cells by regulation of matrix metalloproteinases expression. *Journal of Pharmaceutical Research International*, 33(60), 3901-3908.

Tahmasebi, S., Qasim, M. T., Krivenkova, M. V., Zekiy, A. O., Thangavelu, L., Aravindhan, S., … & Roshangar, L. (2021). The effects of oxygen–ozone therapy on regulatory T-cell responses in multiple sclerosis patients. *Cell Biology International*, 45(7), 1498-1509.

Tan, H., He, Q., Gong, G., Wang, Y., Li, J., Wang, J., … & Wu, X. (2015). miR-382 inhibits migration and invasion by targeting ROR1 through regulating EMT in ovarian cancer. *International Journal of Oncology*, 48(1), 181-190.

Tarugara, A., Mandinyenya, B., & Clegg, B. W. (2023). An outbreak of *Gynanisa maja* (Lepidoptera: Saturniidae) larvae in the southeastern lowveld of Zimbabwe. *Ecology and Evolution*, 13(12).

Thakur, S. K., Natthani, S., & Kotecha, M. (2020). Therapeutic appliance of imperiled medicinal plant Pullas - *Rhododendron arboreum* SM.: A short periodical analysis from ancient to modern era. *International Journal of Ayurveda and Pharma Research*, 8(8), 46-50.

Torre, L. A., Trabert, B., DeSantis, C. E., Miller, K. D., Samimi, G., & Runowicz, C. D. (2018). Ovarian cancer statistics, 2018. *CA: A Cancer Journal for Clinicians*, 68(4), 284-296.

Vang, R., Levine, D. A., Soslow, R. A., Zaloudek, C., Shih, I. M., & Kurman, R. J. (2016). Molecular alterations of TP53 are a defining feature of ovarian high-grade serous carcinoma: A rereview of cases lacking TP53 mutations in The Cancer Genome Atlas ovarian study. *International Journal of Gynecological Pathology*, 35(1), 48-55.

Veerappan, A., Miyazaki, S., & Dhananjayan, R. (2005). Studies on the anti-inflammatory, antipyretic, and analgesic properties of the leaves of *Aegle marmelos* Corr.. *Journal of Ethnopharmacology*, 96(1-2), 159-163.

Visuvanathan, T., Than, L. T. L., Stanslas, J., Chew, S. Y., & Vellasamy, S. (2022). Revisiting *Trigonella foenum-graecum* L.: Pharmacology and therapeutic potentialities. *Plants*, 11(11), 1450.

Vivas-Mejía, P., Benito, J., Fernández, A., Han, H., Mangala, L., Rodríguez-Aguayo, C., ... & López-Berestein, G. (2010). C-jun-NH2-kinase-1 inhibition leads to antitumor activity in ovarian cancer. *Clinical Cancer Research*, 16(1), 184-194.

Waheed, M., Haq, S. M., Arshad, F., Jameel, M. A., Siddiqui, M. H., Bussmann, R. W., ... & Alamri, S. (2023). Where will threatened *Aegle marmelos* L., a tree of the semi-arid region, go under climate change? Implications for the reintroduction of the species. *Land*, 12(7), 1433.

Xu, M., Xiao, J., Chen, M., Liu, Y., Li, J., Shen, H., ... & Yao, S. (2018). miR-149-5p promotes chemotherapeutic resistance in ovarian cancer via the inactivation of the Hippo signaling pathway. *International Journal of Oncology*.

Xu, Y., Gao, W., Zhang, Y., Wu, S., Liu, Y., Deng, X., ... & Sun, L. (2018). ABT737 reverses cisplatin resistance by targeting glucose metabolism of human ovarian cancer cells. *International Journal of Oncology*.

Zakariya, I., Ifezouane, J., Addaoui, A., Skalli, S., & Bouslimane, Y. (2018). Evaluation of the therapeutic and toxicological knowledge of herbalists on the most notified plants in the poison control and pharmacovigilance center of Morocco. *Journal of Pharmacognosy and Phytotherapy*, 10(8), 126-132.