World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Review Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2025
Volume: 4; Issue: 1
Page: 256-265

A REVIEW ON ANTICANCER ARMAMENTARIUM

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Article Received: 05 December 2024 | | Article Revised: 27 December 2024 | | Article Accepted: 19 January 2025

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How to cite this Article: Nidhi Jagtap1, Shital J. Patil (2025). A REVIEW ON ANTICANCER ARMAMENTARIUM. World Journal of Pharmaceutical Science and Research, 4(1), 256-265. https://doi.org/10.5281/zenodo.14785766

ABSTRACT

As one of the biggest causes of death globally, cancer requires the development of efficient treatment approaches. This article offers a thorough analysis of the anticancer properties of several synthetic and natural substances, with an emphasis on paclitaxel, docetaxel, resveratrol, glycyrrhizas acid, and abraxane. These substances show a variety of modes of action, such as the stability of microtubules, the induction of apoptosis, and the modification of signalling pathways, which makes them attractive candidates for cancer treatment. Plant-derived paclitaxel and its abraxane nanoparticle formulation have shown impressive effectiveness against a variety of solid tumors, including lung, ovarian, and breast malignancies. Glycirrhizic acid, a triterpene saponin from liquorice root, has demonstrated potential as a chemotherapy adjuvant by sensitizing cancer cells to chemotherapeutic agents and conquering drug resistance. Resveratrol, a naturally occurring polyphenol found in grapes and berries, has also demonstrated chemo preventive and chemotherapeutic properties. These chemicals have limitations, such as low bioavailability, safety issues, and drug resistance, despite their potential anticancer properties. Future studies should concentrate on creating tailored drug delivery systems, investigating therapeutic combinations that work well together, and carrying out efficacious and safe clinical trials. This review emphasizes the compounds' potential as effective anticancer medicines and stresses the need for more study in this area. In the battle against cancer, interdisciplinary teams and translational research are essential to realizing these substances' full potential and enhancing patient outcomes.

KEYWORDS: paclitaxel anticancer, traditional chemotherapy, mitotic inhibition, neuropathy, multidrug resistance etc.

INTRODUCTION

With an anticipated 19.3 million new cases and about 10 million deaths worldwide in 2020, cancer is still a significant concern (*Cancer Today*, n.d.). Although traditional treatment methods, such as chemotherapy, have helped some cancer patients receive better results their effectiveness is frequently restricted by serious side effects and the emergence of drug resistance (Sung et al., 2021). Thus, the search for new anticancer drugs is desperately needed. Natural suppliers of anticancer drugs may provide enhanced specificity and distinctive modes of action. This thorough analysis looks at the most recent developments on the cancer-fighting abilities of three intriguing natural substances: glycyrrhizin acid, resveratrol, and paclitaxel. Docetaxel, a diterpene that was extracted from the Taxus brevifolia, or Pacific yew tree, is one of among the most often used chemotherapy medications for treating lung, ovarian, and breast malignancies. Even with its therapeutic effectiveness, paclitaxel must be developed into better compositions or dosage forms due to dose-limiting toxicities and increasing drug resistance. Red wine, berries, and grapes all contain resveratrol, a polyphenolic stilbene that has drawn a lot of interest for its complex anticancer properties, which include anti-inflammatory, anti-angiogenic, and antioxidant properties. Triterpenoid saponin glycirrhizic acid, derived from liquorice root (Glycyrrhiza glabra), causes cell cycle arrest and apoptosis in a variety of cancer cell lines, exhibiting specific cytotoxicity. The objective of this study is to present a comprehensive overview of the current knowledge on the pharmacokinetics, clinical trials, and anticancer mechanisms of paclitaxel, resveratrol, and glycirrhizic acid. It will also look at the methods being investigated to optimize their solubility, targeted distribution, and bioavailability for better therapeutic results. This study aims to further the continuous search for safe and efficient natural product-based anticancer treatments by summarizing the existing knowledge.

ANTICANCER ARMAMENTARIUM

1.1 Paclitaxel The mitotic inhibitor

Cancers such as breast, ovarian, and lung are treated with Paclitaxel. It is also used to treat Kaposi's sarcoma related to AIDS. After other treatments fail, Paclitaxel can be given. Paclitaxel is infused slowly into a vein. The infusion usually takes between three and twenty hours to complete. Paclitaxel is usually given every two to three weeks. It will cause you to feel drunk when you are injected with the medicine.

It is a mitotic inhibitor. Drugs known as mitotic inhibitors are made from natural plant sources. They prevent cells from dividing into two genetically identical daughter cells, a process known as mitosis. Tubulin binds to mitotic inhibitors, which prevent tubulin from polymerizing into microtubules. When a cell divides, microtubules are the structures that cause the cell to break apart. Because cancer cells divide (mitotic cell division) more quickly than regular cells, they are more vulnerable to mitotic inhibition. Therefore, cancer cells are more affected by mitotic inhibitors than normal cells. The mitotic inhibitors used in the treatment of cancers vary depending on the type of cancer, such as leukaemia, lymphoma, breast cancer, lung cancer, and others. (Paclitaxel Alternatives Compared)

2. Mechanism of action

Microtubules are one of the key constituents of the cytoskeletal network and are partially responsible for the maintenance of cell shape. They are also the main constituents of the mitotic spindle involved in cell division. In addition to directly interacting with microtubules to stabilize them against depolymerization by cold and calcium, which quickly depolymerize normal microtubules, paclitaxel promotes the polymerization of tubulin to stabilize microtubules. The medicine is distinct from other chemotherapy drugs because it possesses a specific binding site to the

microtubule polymer. It is also uncommon for paclitaxel to polymerize tubulin without the presence of cofactors such as guanosine triphosphate and microtubule-associated proteins (Horwitz, 1994). Paclitaxel has a single set of high-affinity binding sites that allow for selective and saturated attachment to cells. Paclitaxel causes the microtubule cytoskeleton to reorganize, and in cells cultured in tissue culture, large parallel arrays or stable bundles of microtubules form. It prevents cells from forming a typical mitotic apparatus when they are in the G2/M phase of the cell cycle. Paclitaxel preferentially binds covalently to the tubulin beta-subunit when exposed to ultraviolet light along with microtubule proteins. The recent location and cloning of the paclitaxel binding site on beta-tubulin has already shed light on the potential usefulness of radiation and gene therapy that may be employed to provoke or suppress the genetic response towards increasing the susceptibility of cancer cells to paclitaxel. Such combined therapy may in turn provide a new perspective to the treatment of paclitaxel-resistant cancers to minimize the development of multi-drug resistance and to explore the maximum potential of this highly effective drug in the battle against cancer. (Bhat et al., 2020)

3. Pharmacokinetics

Paclitaxel's pharmacokinetics—its absorption, distribution, metabolism, and excretion in the body—have been well investigated. Research has shed light on the nonlinear pharmacokinetics of paclitaxel in mice, emphasizing the effects of varying formulations and doses on the drug's distribution and excretion. Both P-GP and CYP3A4 are effectively inhibited by cyclosporin A (CsA). When CsA and paclitaxel are taken orally together, the latter's bioavailability is greatly increased. Therefore, CsA can be given prior to the oral paclitaxel dose to enhance the drug's systemic absorption. The intravenous formulation containing CrEL is frequently diluted with water when paclitaxel is administered in this manner. After oral dosing, CrEL does not enter the systemic circulation, hence it is unlikely that CrEL would alter the pharmacokinetics of paclitaxel that is absorbed systemically. (De Jonge et al., 2005). Paclitaxel, a chemotherapy agent, has been shown to have several metabolites in human plasma, including alpha-hydroxybutyric acid, 3'-parahydroxybutyric acid, and dihydroxybutyric acid. These studies shed light on paclitaxel's metabolism and the pathways by which it gains its effectiveness (Huizing et al., 1995). The pharmacokinetic profiles of paclitaxel support its potential as an anticancer therapy for solid tumors and leukaemia, either as a monotherapy or as part of a combination regimen (Sonnichsen & Relling, 1994). Furthermore, research has shown that paclitaxel is metabolized in treatment-undergoing patients, with measurable metabolic products in plasma samples. This indicates the drug's biotransformation processes and emphasizes the significance of comprehending the drug's pharmacokinetic behaviour for efficient clinical use (Huizing et al., 1993).

4. Parameters enhancing the action of drug

4.1 Permeability

Several physicochemical investigations demonstrate that hydrophobic pharmaceuticals may be complexed with glycyrrhizic acid to increase the drug's solubility up to 10 times over its initial composition. Because of its propensity to alter membranes, glycyrrhizic acid improves drug entry into cells, therefore increasing the permeability of paclitaxel. Research has demonstrated that glycyrrhizic acid can increase erythrocyte and cell permeability to ions, suggesting that it might affect the permeability of cell membranes. Furthermore, it has been noted that glycyrrhizic acid interacts with lipid bilayers to enhance drug transport through the bilayer and facilitate drug penetration, hence raising paclitaxel's permeability to cells. This process demonstrates the critical function that glycyrrhizic acid plays in enhancing paclitaxel's bioavailability and efficacy through increased cellular absorption (Selyutina & Polyakov, 2019).

4.2 Solubility

Glycyrrhizic acid affects the solubility of paclitaxel by enhancing its solubilization in water. Research has shown that glycyrrhizic acid has solubilization effects on paclitaxel, which can lead to increased concentrations of paclitaxel in water. This interaction between glycyrrhizic acid and paclitaxel plays a crucial role in improving the solubility of paclitaxel, which is essential for its effective delivery and bioavailability (Yang et al., 2015).

4.3 Bioavailability

Many approaches have been investigated to improve paclitaxel's bioavailability. Using nanotechnology is one strategy; paclitaxel-loaded nano sponges (PLN) have demonstrated potential in boosting oral bioavailability without using Cremophor EL. Furthermore, when used with cyclosporin, innovative formulations like Genetaxyl—which contains just 20% CrEL—have been researched to increase oral bioavailability (Yang et al., 2015).An further approach involves the creation of glycyrrhizic acid micelles loaded with paclitaxel, which exhibited a 90% encapsulation efficiency and improved bioavailability via an innovative oral drug delivery mechanism. To increase paclitaxel's oral bioavailability, the co-administration of additional P-glycoprotein efflux pump inhibitors such as cyclosporine and verapamil has also been investigated (Sakr et al., 2021). Through the inhibition of P-GP, the systemic exposure of oral paclitaxel to therapeutic levels is increased by cyclosporine and verapamil, presumably leading to greater bioavailability and better treatment outcomes. This deliberate drug-drug interaction technique seeks to improve the drug's distribution and efficacy by mitigating paclitaxel's low bioavailability, which is a result of its strong affinity for P-gp (Terwogt et al., 1998). Through prospective solutions to enhance the efficacy and distribution of paclitaxel, these techniques hope to improve the results of cancer treatments.

5. Glycyrrhizin acid to prevent paclitaxel induced neuropathy

Glycyrrhizic acid inhibits the absorption of paclitaxel by neurons through the organic anion-transporting polypeptide (OATP), which is the mechanism by which it prevents paclitaxel-induced neuropathy. The main neuronal transporters for paclitaxel have been found to be OATP1A1 and OATP1B2, and glycyrrhizic acid inhibits these transporters, reducing the neurotoxicity that paclitaxel causes. In vivo investigations have shown that glycyrrhizic acid effectively protects against paclitaxel-induced peripheral neuropathy by suppressing the absorption of paclitaxel into neurons through OATP1A1 and OATP1B2 inhibition. This method elucidates the function of glycyrrhizic acid in regulating the uptake of paclitaxel into neurons, presenting a viable approach to alleviate the neurotoxic consequences linked to paclitaxel therapy (Klein et al., 2023).

Peripheral neuropathy, a chemotherapy medication adverse effect that manifests as pain and numbness in the hands and feet, has been linked to paclitaxel. This is because the dorsal root ganglia are an accessible place for paclitaxel to enter and accumulate. Inflammatory reactions, alterations in mitochondrial architecture and function, and impairment of axonal transmission through microtubule stabilization all contribute to paclitaxel's neurotoxicity, which results in degeneration of axonal symmetry and the loss of neural fibres (Zhang et al., 2023). Glycyrrhizic acid inhibits the absorption of paclitaxel by neurons through organic anion-transporting polypeptide (OATP), which is the mechanism by which it prevents paclitaxel-induced neuropathy. The main neuronal transporters for paclitaxel have been found to be OATP1A1 and OATP1B2, and glycyrrhizic acid inhibits these transporters, reducing the neurotoxicity that paclitaxel causes. In vivo investigations have shown that glycyrrhizic acid effectively protects against paclitaxel-induced peripheral neuropathy by suppressing the absorption of paclitaxel into neurons through OATP1A1 and

OATP1B2 inhibition. This method elucidates the function of glycyrrhizic acid in regulating the uptake of paclitaxel into neurons, presenting a viable approach to alleviate the neurotoxic consequences linked to paclitaxel therapy (Klein et al., 2023).

6. Resveratrol in cancer therapy

It has been demonstrated that resveratrol, a naturally occurring stilbene and non-flavonoid polyphenol, possesses antioxidant, anti-inflammatory, cardioprotective, and anticancer qualities. When combined with professionally prescribed medications, it has been shown to reverse multidrug resistance in cancer cells and sensitize them to conventional chemotherapeutic agents. With enhanced resveratrol's anticancer efficacy, absorption, and pharmacokinetic profile, several new analogies have been created. In vitro, the cytotoxic effects of resveratrol have been demonstrated against a wide variety of tumour cells in humans, including skin, lung, and prostate, colon, and breast cancer cells. In animal cancer models, it has also been demonstrated to suppress tumour development and metastasis. Research is being focused on the effects of resveratrol in vivo and in vitro in various cancer types, as well as the intracellular molecular targets that this polyphenol modulates (Ko etal. 2017). Topoisomerase (TOPO) activity, a family of enzymes that control the over- or under-winding of DNA, is blocked by resveratrol as part of its anticancer molecular mechanisms1. It targets developing growth factor-beta (TGF-β) and epidermal growth factor (EGF) and associated receptor (EGF-R), a transmembrane tyrosine kinase triggered by ligands. EGF-R stimulates cell division and development, and aggressive tumour phenotypes usually have elevated expression of this protein. Resveratrol reduces TNF-α-induced inflammation and prevents the expression of NF-κB, a transcription element that is essential for both inflammation and cancer, via acting on the EGF-R pathway. Resveratrol has been proven in multiple research studies to have promise as a cancer therapeutic. It is an intriguing therapy for treating cancer as well as for chemotherapy avoidance. In summary, resveratrol is a potential drug for the treatment and chemotherapy prevention of cancer. Its multifaceted anticancer activity is mediated via several signalling mechanisms that are involved in the development of cancer and the host defensive response. It is a prospective sensitizing agent for adjuvant therapy because of its capacity to raise cancer cell susceptibility to chemotherapeutics and decrease the likelihood of multidrug susceptibility (Varoni et al., 2016).

7. Resveratrol and paclitaxel in combination (case studies)

Case study 1:- This study demonstrated that in HepG2 hepatocyte cancer cells, resveratrol amplifies the anticancer effects of paclitaxel. The results showed that when resveratrol and paclitaxel were coupled, there was a spike in cellular cell death due to elevated ROS levels, activation of radical DNA damage, and improved apoptosis (Jiang et al., 2017).

Case study 2:- This work aimed to overcome multidrug resistance in cancer treatment by introducing a unique technique wherein resveratrol was integrated with paclitaxel in PEGylated lipid particles. Effectively reversing MDR, the integrated liposome demonstrated encouraging outcomes in the simultaneous transportation of both drugs to tumour cells (Meng et al., 2016).

Case study 3:- When paclitaxel and resveratrol were administered together, the resultant oxidative harm to DNA, the rise in ROS levels, and the promotion of apoptosis all contributed to the enhanced cytotoxicity of the cells (Wang et al., 2023).

8. The potential benefits of combining resveratrol and paclitaxel in cancer treatment include

8.1. Improved Anticancer Impacts: Research has indicated that paclitaxel and resveratrol together may boost cellular cytotoxicity, apoptosis, and destruction of DNA, which may improve the treatment's cumulative anticancer efficacy (Wang et al., 2023).

8.2. The stimulation of Anticancer Reactions: It has been observed that resveratrol makes cancer cell lines more susceptible to the anticancer effects of paclitaxel, indicating a potential synergistic impact that might increase the susceptibility of malignant cells to therapy (Jiang et al., 2017).

8.3. Restoration of Multidrug Resistance: New methods utilizing liposomes to co-encapsulate paclitaxel and resveratrol have demonstrated potential in restoring resistance to multiple drugs in cancer treatment, providing a potential way around therapeutic obstacle. Combining paclitaxel with resveratrol may lower the dosage when taken alone, which may have the dual impact of increasing effects and decreasing drug concentration. These lead us to the conclusion that resveratrol may be utilized in conjunction with paclitaxel as a sensitive agent in clinical settings to potentially save lives in the future. (Wang et al., 2023)

8.4. Raised ROS Levels: Resveratrol and paclitaxel together have been linked to higher ROS levels, which may enhance cellular destruction and death and so enhance therapeutic results. (Jiang et al., 2017). All things considered, the combined effect of paclitaxel and resveratrol shows promise for improving the efficacy of chemotherapy for cancer through a number of mechanisms, including enhanced cytotoxicity, treatment sensitization, and resistance to drugs restoration.

9. Interactions of paclitaxel

9.1 Drug-drug interaction (moderate)

9.1.1. With Abraxane: One possible adverse effect of these two drugs is increased risk of nerve injury when using paclitaxel in combination with paclitaxel bound by proteins.

9.1.2 With Dexamethasone: In certain people, dexamethasone could decrease the plasma concentration of paclitaxel, potentially decreasing the effectiveness of the drug in treating cancer.

9.1.3. With probiotic formulas like lactobacillus acidophilus: Patients using paclitaxel may be susceptible to uncommon infections from contact with goods that include live microbes or yeast, contingent upon the dosage and duration of treatment. Unless the body's defence system recuperates from the side effects of paclitaxel, it may be wise to avoid using lactobacillus acidophilus in patients, depending on their general well-being and medical status (*Paclitaxel Uses, Side Effects &Amp; Warnings*, n.d.).

9.2. Drug-food interactions (moderate)

The effects and blood levels of paclitaxel may be enhanced by grapefruit and grapefruit juice. This may raise the possibility of adverse effects including diarrhoea, hair loss, muscular soreness or weakness, nerve damage, and decreased production of various blood cell types due to poor cartilage function (*Paclitaxel Uses, Side Effects &Amp; Warnings*, n.d.).

9.3. Drug disease interactions (major)

9.3.1. Infections: In addition to their cytotoxic effect, anti-cancer agents can induce myelosuppression when they act on tissue. If you have a known infectious disease, you may not be able to use these drugs.

9.3.2. Conduction disorder (arrhythmia): It has been reported that paclitaxel can cause severe conduction abnormalities, including the need for pacemakers. A patient with a conduction disorder or one predisposed to such a disorder should take caution when receiving paclitaxel therapy. During subsequent therapy with paclitaxel, cardiac function should be monitored clinically.

9.3.3. Hepatic dysfunction: The liver undergoes considerable metabolism of paclitaxel. Hepatotoxicity may be more common in patients with moderate to severe liver dysfunction. Additionally, individuals with blood bilirubin concentrations >2 times ULN may experience worsening myelotoxicity from paclitaxel. Patients with impaired liver function should receive paclitaxel therapy with caution and at a dose that is lower.

9.3.4. Peripheral neuropathy: During paclitaxel treatment, 60% of patients have been observed to have been influenced by dose peripheral nerve damage. In rare cases, severe nerve damage necessitates a 20% decrease in the paclitaxel dose. Paclitaxel therapy should be used with caution in individuals who have nerve damage or who are at risk of developing it.

10. Alternative to Paclitaxel

10.1. Docetaxel

The semi-synthesis of 10-deacetylbaccatine III, or 10-DAB, from the typical Taxus baccata, or English yew, yields docetaxel. A well-known example of the value of pharmacognosy in the pursuit and creation of novel medications is this one. There are two noteworthy facts: First, paclitaxel was discovered using bark extracts from the Pacific yew (Taxus brevifolia). This substance shows a strong anti-tumour effect against certain kinds of cancer. The primary problem with paclitaxel as a medicinal agent is that it was only derived from aged yew trees. The tree is killed when its bark is harvested. This notion was not viable since the age at which a tree could produce its greatest yield was too high. For those working in synthetic chemistry, paclitaxel's intricate structure poses a significant hurdle. However, Taxus baccata was the source of the answer. This yew's needles yield the compound 10-DAB, which is the most complicated residue of paclitaxel Strong chemotherapeutic drugs, paclitaxel and docetaxel, impede tubulin depolymerization, which inhibits spindle motility and triggers cell cycle arrest (*Docetaxel - Search Results. Page 1 of About 968 Results*, n.d.). Despite having the same tubulin binding site, docetaxel and paclitaxel are not the same pharmacologically. In clinical trials, individuals with platinum- and paclitaxel-resistant ovarian cancer showed respectable rates of reaction and a manageable safety profile when treated with docetaxel alone. Specifically, docetaxel has a low incidence of neurotoxicity, a common side effect of both paclitaxel and cisplatin, which makes it a viable agent for coupling cisplatin with other platinum compounds (Katsumata, 2003).

10.2. Abraxane

In patients with early-stage breast cancer, Abraxane provides higher pathological total improvement rates than Taxol when administered prior to surgery. Compared to Taxol, Abraxane (chemically: albumin bound or nab paclitaxel) is a distinct version of the drug. The medications in question are taxanes, an effective class of chemotherapy drugs that prevent cancer cells from proliferating and mend themselves. Previous studies have demonstrated that in the treatment

of metastatic breast carcinoma, Abraxane is more advantageous than a solvent-based taxane. According to another trial, chemotherapy with a taxane and an anthracycline combination provided superior pathologic complete response rates for managing the initial stages of breast cancer before operations than chemotherapy with an anthracycline and a taxane combination (Abraxane *Offers More Benefits than Taxol When Given before Surgery to Treat Early-Stage Disease*, 2022).

11. Pregnancy warning

Research on animals has demonstrated that this medication is both fetotoxic and embryotoxic. For human pregnancy, there are few controlled studies availableIn pregnant women, this medication may have harmful effects on the developing foetus. Intrauterine mortality, higher resorptions, and increased foetal fatalities show that administration of 3 mg/kg/day roughly 0.2 the daily maximum permitted human dosage on an mg/m2 basis to rabbits during organogenesis induced embryotoxicity and foetal toxicity. At this level, maternal damage was also noted. At 1 mg/kg/day, no teratogenic consequences were seen; however, because of widespread foetal death, it was not possible to evaluate the teratogenic potential at higher dosages.

CONCLUSION

In this review, we have thoroughly investigated the potential benefits of several synthetic and natural substances as anticancer medicines, with a particular emphasis on paclitaxel, docetaxel, resveratrol, glycirrhizic acid, and abraxane. These substances have shown encouraging anticancer properties via a variety of methods, such as signal pathway modification, apoptosis induction, and maintaining microtubule stability.

Clinical trials on a variety of solid tumors, including lung, ovarian, and breast malignancies, have demonstrated the exceptional effectiveness of paclitaxel and its nanoparticle version, abraxane. However, side effects and medication resistance frequently restrict their clinical use. The natural antioxidant resveratrol has demonstrated chemo preventive and chemotherapeutic effects; however, its bioavailability is still a problem. Triterpene saponin glycirrhizic acid has shown promise as an adjuvant treatment by overcoming drug resistance in cancer cells and sensitizing them to chemotherapeutic drugs.

Even with the encouraging outcomes, several issues still need to be resolved. These include reducing toxicity to healthy cells, conquering ways to resist, and improving drug delivery methods. Subsequent investigations have concentrated on investigating the synergistic pairings of these substances with current treatments, clarifying their molecular modes of action, and carrying out clinical studies to assess their safety as well as effectiveness.

The creation of tailored and targeted anticancer treatments is still a top objective, and the substances included in this review have a lot of promise to help with this effort. Sustained investigations in this domain are essential for enhancing patient results and propelling the battle against cancer. For the sake of patients everywhere, interdisciplinary cooperation between scientists, physicians, and business partners will be crucial to converting these potential anticancer drugs into successful treatments.

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