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RUBIADIN: UNVEILING ITS PHOTODYNAMIC MECHANISMS FOR CANCER THERAPY

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ABSTRACT

Cancer, characterized by uncontrolled cell proliferation and metastasis, remains a major global health challenge with significant mortality and morbidity. Traditional therapies, including chemotherapy and radiation, often exhibit severe adverse effects, toxicity to healthy tissues, and the rapid emergence of drug resistance. These limitations have driven the exploration of natural products as alternative therapeutic agents due to their multi-target capabilities, reduced toxicity, and cost-effectiveness. Rubiadin, an anthraquinone derivative obtained from *Rubia cordifolia*, has emerged as a promising candidate for cancer treatment. It exhibits a wide range of pharmacological activities, including antioxidant, anti-inflammatory, and neuroprotective effects. Its unique potential lies in photodynamic therapy (PDT), a targeted approach that uses light-activated photosensitizers like rubiadin to generate reactive oxygen species (ROS), including singlet oxygen. This process selectively induces cancer cell death through apoptosis, necrosis, or autophagic pathways, minimizing damage to healthy tissues. Rubiadin also shows efficacy against chemotherapy resistance and metastasis. However, challenges such as genotoxicity, limited bioavailability, and toxicity at higher doses highlight the need for further research. Strategies including combinatorial therapies, targeted delivery systems, and the development of structural analogs are essential to optimize rubiadin's therapeutic potential. This review underscores the importance of natural products in modern oncology and positions rubiadin as a cornerstone

for advancing next-generation cancer therapies, particularly through its application in photodynamic therapy (PDT).

KEYWORDS: Cancer therapy, Metastasis, Photodynamic therapy, Rubiadin.

1 Overview of cancer

Cancer involves uncontrolled cell growth and metastasis, driven by genetic, immune, and hormonal factors, as well as external triggers like radiation, chemicals, and infections. Lifestyle factors and pollutants also heighten risk.[1] Cancer poses a significant health challenge in India, with 2-2.5 million cases and 7 lakh new cases annually, leading to 3 lakh deaths and 15 lakh requiring comprehensive care.[2] Global cancer prevalence in 2008 estimated 12.66 million new cases, with Asia contributing 48%. Stomach, colorectal, lung, and breast cancers dominated globally, while the UK faced mostly breast, lung, colorectal, and prostate cancers.[3] In 2008, international age-standardized incidence rates showed that men (204 per 100,000) were more likely than women (165 per 100,000) to develop cancer.[4] In 2020, there were 19.3 million new cancer cases and 10 million deaths, with cases projected to reach 28.4 million by 2040. Breast, lung, and colorectal cancers were most common, and high-income countries had higher incidence rates. The rise in cancer cases is driven by population changes and increasing rates of six major cancers. The WHO identifies cancer as a leading global health risk, emphasizing the need for early detection, prevention, and improved patient care.[5]

Cancer encompasses over 277 diseases marked by uncontrolled cell growth, driven by various factors and mechanisms.[6] Cancer develops in three stages: initiation, where genetic mutations occur; promotion, where cells become malignant; and progression, where tumors grow and cells divide uncontrollably. The ability of cancer cells to spread beyond their origin contributes significantly to its severity and fatality.[7]

Cancer research is highly complex due to the vast differences in genetic changes, affected organs, prognosis, and treatment approaches across various cancer types.[8] Cancer treatment success depends on the type and stage of the disease. Options include surgery, chemotherapy, radiation, and immunotherapy, tailored to each patient's specific case.[9]

Chemotherapy, a systemic treatment, uses cytotoxic agents to disrupt the cell cycle, targeting fast-growing cancer cells. Unlike chemotherapy, radiation and surgery primarily affect

localized areas. The rapid proliferation of cancer cells makes them more vulnerable to chemotherapeutic agents.[10] Cancer drugs are categorized into five main groups based on their molecular properties: alkylating agents like cisplatin, antimetabolites such as 5-fluorouracil, tubulin-binding drugs like paclitaxel, antitumor antibiotics like doxorubicin, and topoisomerase inhibitors like topotecan.[11]

Chemotherapy, while effective, causes serious adverse effects such as myelosuppression, alopecia, mucositis, severe nausea, and vomiting. Additionally, multidrug resistance (MDR) cancer is a major challenge, responsible for over 90% of cancer-related deaths following treatment.[12]

Small molecule targeted therapy (SMTT) offers an alternative cancer treatment by using substances that target specific molecular elements in cancer cells. These targets, often genetically altered, are crucial for tumor growth and survival, frequently involved in disrupted signaling pathways during cancer development.[13]

Targeted therapies like imatinib, carfilzomib, and ribociclib are used to treat cancer, offering more specific action on cancer cells compared to traditional treatments. However, they can still cause side effects like rashes, diarrhea, hypertension, and may lead to drug resistance over time.[14]

While effective, cancer treatments like chemotherapy and radiation have significant drawbacks, including severe adverse effects like hair loss, pain, nausea, and fatigue. Additionally, these treatments can damage both healthy and cancerous cells, leading to hematological toxicities and tissue damage, making cancer difficult to treat due to its heterogeneous nature.[15]

Platinum-based chemotherapy drugs like cisplatin, carboplatin, and oxaliplatin damage DNA by inhibiting nucleotide synthesis. Tyrosine kinase inhibitors (e.g. icotinib, erlotinib, gefitinib) target specific proteins, while drugs like bevacizumab, sunitinib, and sorafenib work by reducing angiogenesis.[16]

Natural products are gaining attention as potential cancer treatments due to their ability to target multiple oncogenic pathways, including angiogenesis, apoptosis, and cell proliferation. They can enhance chemotherapy effectiveness, particularly in drug-resistant cases, and

favored for their low toxicity, safety, affordability, and environmental benefits compared to synthetic drugs.[17]

2 Natural anti-cancer agents

Natural products (NPs) from bacteria, plants, and animals are key in drug development, comprising 32% of small-molecule drugs since 1981. With 547 FDA-approved NPs, they significantly aid in treating hypertension, infections, and cancer.[18,19,20] With over 350,000 vascular plant species, plants provide diverse bioactive compounds like alkaloids, terpenes, and flavonoids. These serve as medicines or precursors for synthetic drug development[21,10] Berberine, a phytochemical from Berberis plants, showed promising results in treating cancer, metabolic dysfunction, inflammation, and neurological and cardiovascular diseases, based on preclinical research and limited human studies.[22,23] Natural substances, with complex, rigid structures, excel in treating diseases like cancer and infections. Their historical use and chemical diversity surpass traditional synthetic libraries, aiding effective drug development.[24] Natural compounds are vital in anticancer therapy, forming the basis of half of cancer drugs, like paclitaxel and vincristine. Semi-synthetic derivatives like docetaxel and etoposide further enhance cancer treatment efficacy.[25,26] Natural substances aid cancer prevention by targeting pathways like PI3K and MAPK. Curcumin, a key phytochemical, modulates NF-κB and p53, showing potential for chemopreventive effects.[27,28]

2.1 Anti-Chemoresistance natural products

Chemoresistance, driven by mechanisms like drug efflux and epigenetic changes, poses a major challenge in cancer treatment, often leading to metastasis and recurrence. Phytochemicals, with their natural properties, offer a promising solution to overcoming chemoresistance and reducing the toxicity of conventional chemotherapies.

- **Lupeol:** It has been shown that this natural substance can sensitize therapy-resistant cancer cells. It does this via regulating important pathways involved in the regulation of the cell cycle as well as a number of inflammatory cytokines.
- **Shikonin:** Shikonin, a naturally occurring naphthoquinone, effectively reverses drug resistance in a range of cancer cell types by causing necroptosis. It targets proteins like Bcl-2 and P-glycoprotein that are implicated in drug resistance pathways.[29]
- **Pterostilbene:** By down regulating particular chemoresistance-related pathways, this chemical reduces drug resistance mechanisms and causes S-phase cell cycle arrest, death, and autophagy.[30]

- **Epigallocatechin Gallate (EGCG):** It is well established that EGCG causes G2/M cell cycle arrest and lowers cancer cell levels of treatment resistance. Because of this characteristic, it could be a good option to enhance the results of chemotherapy.[31]
- **Plumbagin:** Plumbagin targets several pathways related to angiogenesis, apoptosis, autophagy, and cell cycle regulation. In addition, it damages DNA and causes oxidative stress in cancer cells, which enhances its anti-chemoresistance qualities.[32]
- **Quercetin:** This naturally occurring flavonoid alters the RAGE/PI3K/AKT/mTOR axis, which in turn promotes cell death and chemosensitivity. It focuses on signaling pathways that are essential to chemoresistance.[33]
- **Ferulic Acid:** Ferulic acid has demonstrated the ability to reverse P-glycoprotein-mediated multidrug resistance by blocking the PI3K/AKT/NF-κB pathway, a key player in the development of chemoresistance.[34]

2.2 Anti-Metastasis natural products

Metastasis, a key factor in cancer mortality, involves the spread of tumor cells to other organs. Natural substances have shown promise in addressing metastasis, with several compounds demonstrating potential to inhibit tumor progression and the formation of secondary tumors.

- **Apigenin:** Apigenin is one phytochemical that possesses antimetastatic properties. It impacts the primary epigenetic mechanisms that regulate genes linked to metastasis, including DNA methylation, histone modifications, and non-coding RNA-associated multigene suppression.[35]

2.3 Combining natural products with chemotherapeutic drugs

Combinatorial therapy, which combines natural substances with conventional chemotherapy, helps to overcome drug resistance, enhances treatment efficacy, and reduces toxicities. This approach has shown great results in improving cancer treatment outcomes.

- **Silybinin:** This organic substance effectively overcomes drug resistance by sensitizing colorectal cancer cells to doxorubicin through GLUT1 expression inhibition. It presents a possible way to raise the effectiveness of chemotherapy medications.[36]
- **Curcumin:** It has been demonstrated that curcumin increases the anti-tumor efficacy of doxorubicin, which makes it a desirable choice for combinatorial therapy. Combining these two has produced encouraging outcomes in preclinical models.[37]

- **Resveratrol:** Resveratrol and paclitaxel work synergistically to cause oxidative stress and apoptosis via activating the TRPM2 channel. This implies that resveratrol, when paired with other chemotherapeutic drugs, may improve the effectiveness of cancer treatment.[38]
- **Noscapine:** It's been demonstrated that noscapine can make cisplatin more sensitive by influencing the cell cycle and causing apoptosis in cisplatin-resistant cells, like ovarian SKOV3 cells.[28]
- **Neferine:** Neferine stops the cell cycle and encourages the overproduction of ROS in lung cancer cells, which enhances the anticancer activity of cisplatin.[39]
- **Cryptotanshinone:** Cryptotanshinone, when coupled with paclitaxel, causes apoptosis by blocking the JAK/STAT3 signaling pathway and prevents tongue squamous cell carcinoma cell lines from migrating and proliferating.[40]

2.4 Anticancer agents: Marine natural products

Naturally occurring marine compounds, including terpenoids and alkaloids, have shown potential against various cancers like breast adenocarcinoma and hepatocellular carcinoma. These compounds target key biological pathways such as ER stress, apoptosis, and inflammation, offering new avenues for cancer treatment.[41] Studies have shown that aplysinopsin derivatives, particularly the EE-84 homologue, may effectively treat chronic myeloid leukemia by inducing cytostatic effects, autophagy, and ER stress. Additionally, astaxanthin, a pigment from marine organisms, has demonstrated the ability to inhibit prostate cancer growth and reduce stemness markers in breast cancer cells, leading to decreased invasiveness and induced apoptosis.[42] Research on flaccidoxide-13-acetate, a diterpenoid from the marine coral *Sinularia gibberosa*, revealed its potential to inhibit hepatocellular carcinoma (HCC) metastasis by targeting cell survival, motility, and invasion. Additionally, an extract from *Penicillium purpurogenum* demonstrated anticancer effects in a mouse model, reducing tumor inflammation and necrosis without adverse effects.[43,44] The discovery of novel marine compounds with potent cytotoxic properties, such as those from *Penicillium chrysogenum* and *Sarcophyton digitatum*, which showed effectiveness against hepatocellular carcinoma and breast cancer cells. The challenges such as low extraction yields, offering solutions like chemical modification, genetic engineering, and optimized synthesis methods for compounds like nannocystin A are also addressed.[45,46,47,48] The marine natural products are promising cancer therapies, addressing various study findings and strategies to overcome extraction challenges and are potential in advancing cancer treatment options.[49]

3 Anthraquinone overview

Anthraquinone is a complex chemical with diverse biological applications, particularly in cancer treatment. Its unique structural features, including carbonyl groups at specific positions, make it a significant subject of pharmacological research due to its rigidity, planarity, and aromaticity.[50]

Anthraquinone's planar structure allows it to intercalate with DNA, making it a key feature in the development of anticancer drugs. Natural compounds like emodin, aloe-emodin, rhein, and chrysophanol, which contain anthraquinone, serve as the foundation for various anticancer medications.[51]

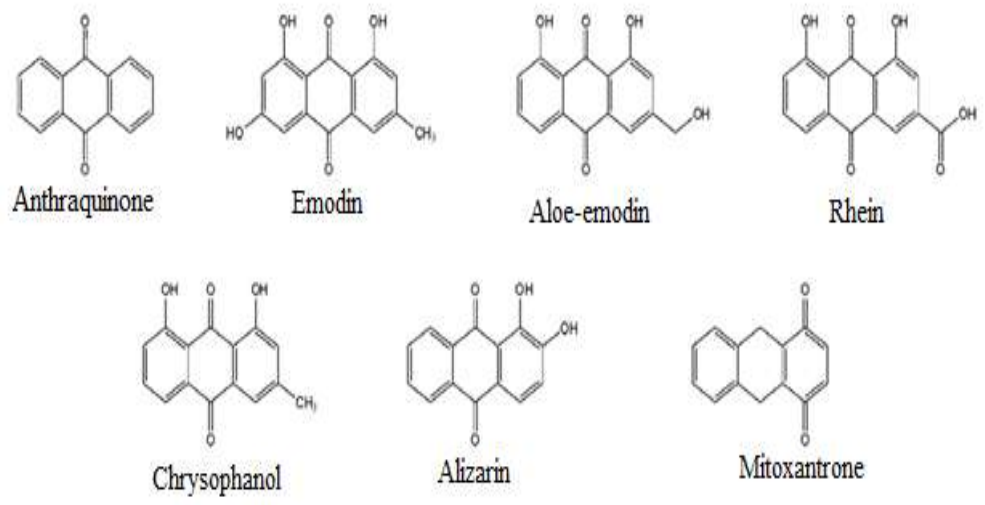

Fig. 1: Anthraquinone molecules found in nature from various sources.

Anthraquinones have a rich history dating back to the 1800s, starting with pioneering research on the oxidation of anthracene to produce anthraquinone. This discovery laid the foundation for their use in various applications, including anticancer treatments.[52] Later researchers made significant contributions by linking anthraquinone to alizarin and proposing its exact structure. Over time, natural anthraquinones have been discovered in over 75 environments, including lichens, marine life, fungi, and medicinal plant.[53,54]

Various synthetic methods, including Diels-Alder cycloaddition, intramolecular cyclization, and iridium-catalyzed pathways, have enabled the production of diverse anthraquinone derivatives, many of which show promise in cancer treatment. Beyond medicine, anthraquinones are widely used in textiles, paints, cosmetics, and other industries.[55,56,57,58,59]

Anthraquinones are versatile compounds with a wide range of pharmacological properties, including laxative, antidiabetic, neuroprotective, antiviral, antimalarial, and antifungal activities. They also serve as catalysts in chemical and biogeochemical processes, particularly in pollutant breakdown.[60,61,62,63,64]

Anthraquinones, with their rigidity and planarity, are emerging as promising candidates for anticancer drugs, such as doxorubicin, mitoxantrone, and epirubicin. Research into novel anthraquinone derivatives continues to grow, highlighting their potential to inhibit cancer cell proliferation, invasion, and metastasis, while also functioning as anti-inflammatory, antioxidant, and immune modulatory agents. These compounds also show potential in overcoming multidrug resistance in tumors and targeting cancer-related proteins and enzymes.[65] In conclusion, anthraquinones are a promising class of compounds with significant potential in anticancer drug development. Ongoing research aims to enhance their therapeutic benefits while minimizing adverse effects, making them a dynamic area of pharmacological study.[66]

4 Ribiadin: Pharmacological overview

Rubiadin, derived from *Rubia cordifolia* of the *Rubiaceae* family, is known for its wide range of pharmacological properties, including antiviral, antibacterial, antimalarial, antifungal, hepatoprotective, neuroprotective, anti-inflammatory, antioxidant, and anticancer effects. However, despite its therapeutic potential, it has not yet undergone comprehensive evaluation.[67]

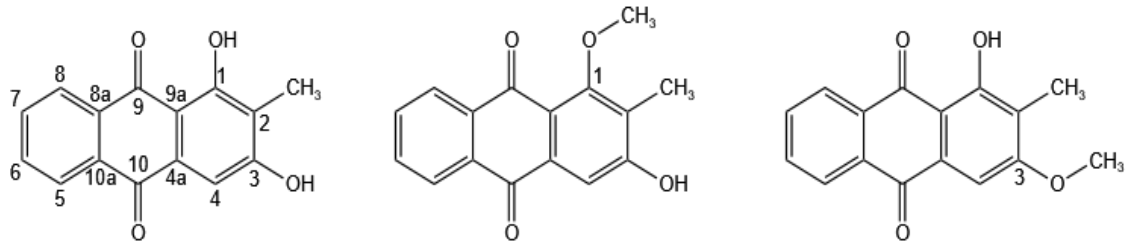

Fig. 2: Rubiadin and Its analogues.

4.1 Toxicity

When evaluated for toxicity prediction under OECD guidelines, rubidin demonstrated a high safety margin. Oral administration to rats did not cause any appreciable harm, with LD_{50} values exceeding 7000 mg/kg, as reported in software studies and supported by research

involving *Rubia cordifolia* and *Rubia tinctorum* extracts, which confirmed its safety at various dosing levels.

4.2 Anticancer and Photodynamic therapy

Rubiadin shows promise as an anticancer agent by inducing apoptosis, cell cycle arrest, and DNA damage, and also acts as a photosensitizer in photodynamic therapy. However, concerns about its potential carcinogenicity, particularly in madder dye, have been raised.[51,68,69,70,71]

4.2.1 Antiosteoporotic activity

Rubiadin from *Rubia cordifolia* extract inhibits excessive bone resorption by blocking the NF-κB pathway and osteoclast-related proteins, while increasing osteoprotegerin levels. However, further research is needed to fully understand its antiosteoporotic effects before human trials.[72,73]

4.2.2 Anti-Inflammatory activity

Rubia cordifolia extract (RBME) effectively suppressed pro-inflammatory markers in models of acute lung injury and macrophages, showing potential anti-inflammatory benefits. However, further research is required to confirm the specific anti-inflammatory actions and mechanisms of rubiadin.[74,75]

4.2.3 Anti-diabetic activity

Rubiadin-loaded niosomes (RLN) significantly reduced blood glucose levels and improved metabolic markers in rats with diabetic nephropathy. However, further research is needed to confirm it’s antidiabetic effectiveness and potential therapeutic benefits for diabetes.[76]

4.2.4 Hepatoprotective activity

Rubiadin showed potential hepatoprotective effects by reducing hepatic malondialdehyde levels and normalizing liver indicators in rats with CCl4-induced liver injury. However, further research in human-relevant models is needed to confirm its efficacy.[67]

4.2.5 Neuroprotection

Rubiadin demonstrated potential anticonvulsant effects by significantly reducing seizures in mice, suggesting its neuroprotective properties. This opens avenues for exploring its efficacy in treating neurodegenerative diseases like Parkinson's, Alzheimer's, and Huntington's.

4.2.6 Antioxidant activity

Rubiadin exhibits strong antioxidant properties, particularly by inhibiting lipid peroxidation induced by ferrous sulfate and t-butylhydroperoxide, especially in the presence of Fe^{2+}. It demonstrates stronger antioxidant effects than many other compounds. However, further in vivo and in vitro studies are needed to fully evaluate its antioxidant potential and confirm these findings across different models.[77,78]

4.2.7 Antifungal activity

Rubiadin, found in Rubia cordifolia extract, shows significant antifungal properties, particularly against *Candida tropicalis* and other pathogens like *Aspergillus* species. It prevents biofilm formation and, when combined with amphotericin B, exhibits a synergistic effect, highlighting its potential as a lead compound for antifungal drug development.[79,80,81,82]

4.2.8 Antimalarial, Antibacterial and Antiviral Activities

Rubiadin displays strong antimalarial activity against *Plasmodium falciparum* and antibacterial effects against *Staphylococcus aureus*. Rubiadin also shows promise as an anti-hepatitis B virus (HBV) agent by inhibiting HBV DNA replication and lowering viral markers.[83,84,85,70]

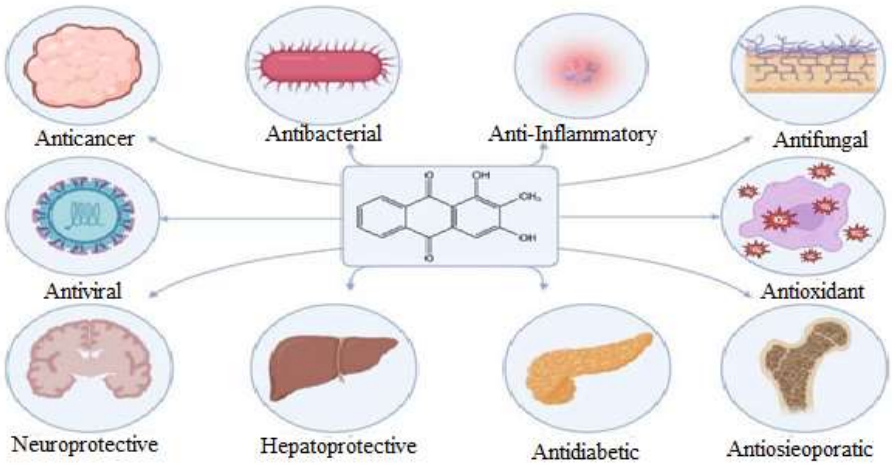

Fig. 3: The biological Characteristics and Possible medicinal benefits of rubiadin.

5 Rubiadin sources

Rubiadin, derived from *Rubia cordifolia*, is a natural compound valued in Ayurveda for its therapeutic properties.[67] *Morinda officinalis*, a traditional Chinese herb, is a key source of

rubiadin and is widely used in Chinese medicine for its therapeutic benefits.[29] Rubiadin is a key component of Ayurvedic preparations like Manjisthadi churna, used for treating hyperlipidemia and other ailments.[86] Rubiadin is a component of traditional Chinese formulations like Jia-Jian-Di-Huang-Yin-Zi and Er Xian decoction, offering therapeutic benefits.[87,88] Rubiadin is a vital compound in traditional medicine, valued for its versatility in treating various ailments across Ayurveda and Chinese medicine.

5.1 Uses

Rubia cordifolia, or Indian Madder, is widely used for its anti-inflammatory, antioxidant, and antimicrobial properties. It is a potent blood purifier, supports skin health, and promotes wound healing. Additionally, it offers hepatoprotective, antidiabetic, and anticancer potential, making it a versatile plant in traditional and modern medicine.[89,90,91,92]

5.2 Structural characteristics

A detailed structural analysis of rubiadin, using techniques like 13C-NMR, 1H-NMR, FTIR, UV, and EI-MS, reveals key spectral features such as absorption maxima at 251 nm and 408 nm, characteristic infrared bands, and specific NMR signals. The analysis confirms its molecular formula as C15H10O4, with distinct signals for the anthraquinone nucleus and aromatic ring structure.[85]

Table 1: Spectroscopic data for rubiadin.

Spectroscopic Method	Data
UV SPECTRA	λmax at 408 nm (n-π* transition), 279 nm, and 251 nm (π-π* transitions)
FTIR SPECTRA	3396 cm-1 (OH), 2923 cm-1 (C-H), 1661 cm-1 (non-chelated C=O), 1623 cm-1, and 1589 cm-1 (C=C in the aromatic ring) are the absorption bands.
EI-MS	Molecular formula C15H10O4, molecular ion peak at m/z 254.12
1H-NMR SPECTRUM	- Hydroxyl group linked to hydrogen at δ 13.06 (1H, s) - Phenolic hydrogen (1H, br.s) at δ 11.22 - Singlet at δ 2.02 (aromatic ring methyl group attached) - Singlet at δ 7.1 (position of an aromatic proton in H–4) - A multiplet with two protons (aromatic protons at H-6 and H-7 locations) between δ 7.83 and 7.88 - A pair of doublet of doublets for H-8 and H-5, respectively, at δ 8.08 (dd, 1H, J = 1.5, 7.5 Hz) and 8.12 (dd, 1H, J = 1.5, 7.5 Hz).
13C-NMR SPECTRUM	- 15 signals, including two conjugated carbonyl carbon signals at δ 186.2 and 181.78. - Signal (methyl carbon) at δ 8.09 -Signal (C-2 carbon) at δ 108.9. - Adjacent carbon atoms at δ 107.35 (C-4) and 117.3 (C9a), with two phenolic carbons at δ 162.82 and

	162.46. -The anthraquinone system's unsubstituted aromatic ring is represented by the remaining signals at δ 134.54 (C-8a), 134.44 (C10a), 132.98 (C-4a), 132.87 (C-6), 131.70 (C-7), 126.70 (C-5), and 126.37 (C-8).

5.3 Synthesis

The synthesis of rubiadin involves two steps, as mentioned in the original article. The first step involved condensing phthalic anhydride (1) and 2,6-dihydroxytoluene (2) with CH2ClCH2Cl/CHCl2CHCl2 in the presence of aluminum chloride to form the molecule known as 2-(2′,4′-dihydroxy-3′-methyl) benzoylbenzoic acid (3) [Step 1].

In the second stage, molecule 3 goes through a cyclization process. The dehydration procedure, which is conducted for 25 minutes at 100 °C in the presence of fused boric acid and concentrated sulfuric acid, completes this cyclization. This second phase results in the formation of rubiadin [Step 2].[93]

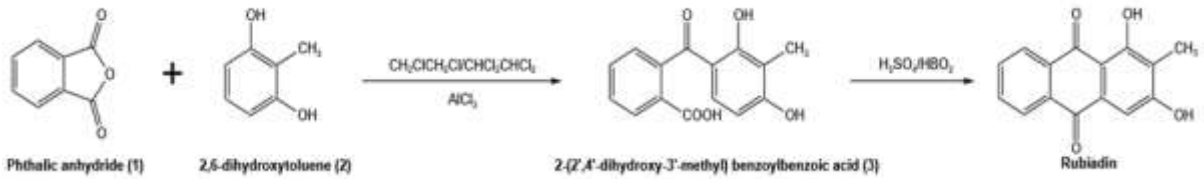

Fig 4: Synthesis of rubiadin.

5.4 PK of Rubiadin

A study using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) investigated the pharmacokinetics of rubiadin and RBME in Morinda officinalis. The research showed that salt-processed Morinda officinalis (SMO) significantly enhanced the bioavailability of rubiadin and RBME, as indicated by higher Cmax and AUC0-t values. Rubiadin reached its peak concentration after 1.5 hours, with the highest concentrations found in the small intestine. However, further research is needed to fully understand the pharmacokinetic profiles of rubiadin.[29,94]

5.5 ADMET Properties

The ADMET properties of rubiadin were analyzed using the vNN-ADMET website, revealing potential hepatotoxicity, rapid digestion, and possible drug-drug interactions due to inhibition of certain cytochrome P450 enzymes. The compound was not predicted to affect membrane transporters like P-glycoprotein or the blood-brain barrier. However, rubiadin may

have mutagenic effects and mitochondrial toxicity, raising concerns about its safety. The estimated oral rat LD50 values suggest 7000 mg/kg.[95,96]

6 Anti-cancer action of rubiadin

Photodynamic therapy (PDT) involves the use of a photosensitizer (PS) that accumulates in cancer cells and is activated by light of a specific wavelength. This activation produces reactive oxygen species (ROS) such as singlet oxygen and hydroxyl radicals, which induce cytotoxicity, leading to the destruction of targeted tissue.[97,98,99]

Photodynamic therapy (PDT) offers advantages over traditional cancer treatments by selectively targeting cancer cells while minimizing damage to healthy tissue. The therapy's specificity relies on the photosensitizer's natural accumulation in tumor tissues and the precise application of light to the targeted area, either topically or intravenously.[100] PDT not only targets tumors by rupturing blood vessels and increasing oxidative stress but also enhances anti-tumor immunity, offering potential for long-term disease control. Compared to traditional therapies, PDT is more cost-effective and often has a stronger immunomodulatory effect.[101]

PDT can cause side effects like skin redness, stinging, swelling, pain, and elevated blood pressure due to intense radiation therapy.[102,103] In PDT, the photosensitizer absorbs light, transitioning to an excited state and triggering photochemical reactions. These reactions can be Type I, producing radicals and reactive oxygen species (ROS), or Type II, where energy is transferred to oxygen to produce singlet oxygen, leading to cell death.[104,105,99] In PDT, the mode of cell death depends on the photosensitizer and treatment parameters. Moderate damage typically induces apoptosis, while high doses can lead to necrosis or autophagic cell death, with autophagy potentially serving as a protective mechanism. Photodamage from PDT can trigger apoptosis through processes like cytochrome c release and mitochondrial damage, while high-dose therapy can cause necrosis, characterized by lysosomal rupture, cell swelling, and inflammation. The extent of autophagy depends on the photosensitizer's location and dosage, influencing cell survival or death.[106,107]

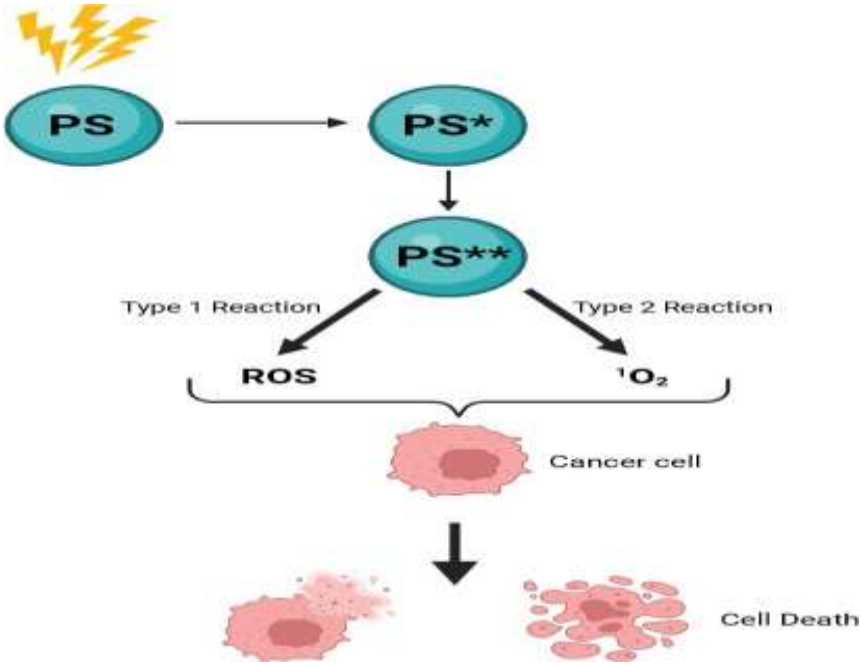

Fig. 5: Mechanism of photodynamic therapy.

{PS – Photosensitive, PS* - PS with excited singlet state, PS - PS with excited triplet state, ROS - Reactive oxygen species, $^1O_2$ - singlet oxygen}**

Rubiadin has shown potential anticancer properties by inducing DNA damage, arresting the cell cycle, and triggering apoptosis, which can halt uncontrolled cancer cell growth and lead to their elimination.[51]

Recent research has demonstrated that rubiadin has photosensitizing properties, effectively killing human breast cancer (MCF-7c3) and colon cancer (SW 480) cells when activated by light. The treatment resulted in reduced cell viability and singlet oxygen production, indicating rubiadin's potential as a photodynamic therapy agent for cancer cell destruction.[90,52] Studies have shown that rubiadin induces apoptosis in cancer cells through mechanisms such as DNA fragmentation, PARP cleavage, and caspase-3 activation. These findings reveal the molecular processes behind rubiadin's antitumor effects. Rubiadin shows significant cytotoxicity against various cancer cell lines, including HepG2, MCF-7, and HeLa, with promising IC50 values. However, studies indicate its potential carcinogenicity, particularly in the liver and kidneys, where it may accelerate the development of preneoplastic lesions and enhance tumor growth.[109]

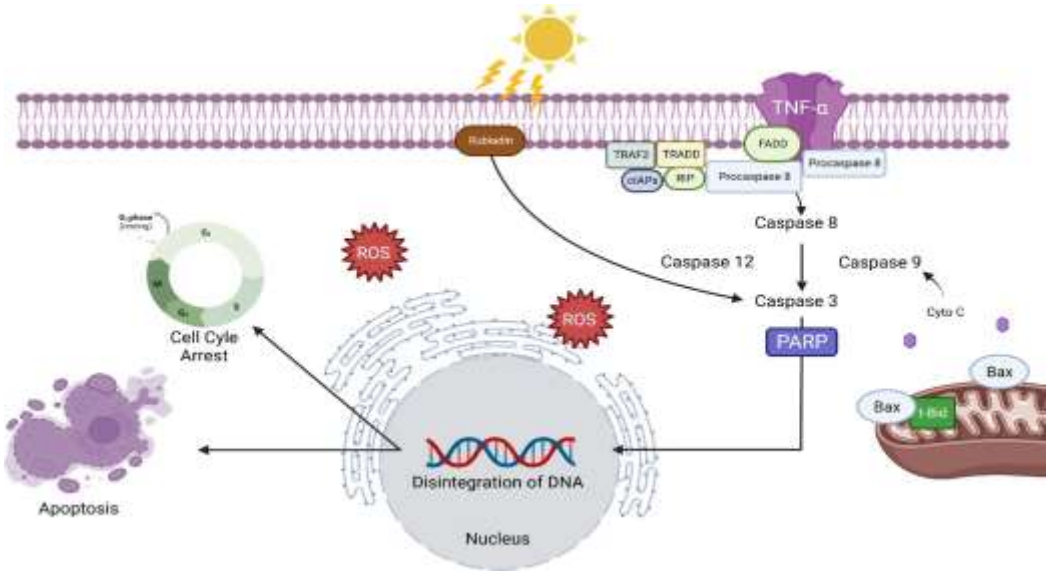

Fig. 6: Rubiadin can be utilized in photodynamic Treatment and Has the favorable photosensitizing capacity to serve as an anticancer agent, principally through DNA damage, cycle Arrest and Apoptosis.

Rubiadin and related compounds may be excreted in rat urine after the administration of lucidinprimeveroside (Lup), with rubiadin shown to be more effective than lucidin at inducing DNA synthesis in rat hepatocytes. These findings raise concerns about the potential genotoxicity of these substances.[110] Novel anthraquinones like rubiadin may inhibit cancer through mechanisms such as paraptosis, autophagy, and radiosensitization, potentially addressing chemotherapy resistance.[51] In conclusion, while rubiadin shows potential as an anticancer agent, its effects may vary and could be carcinogenic in certain cases, highlighting the need for further research. Photodynamic therapy, with its low side effects and high selectivity, offers a promising cancer treatment option.[111]

Consumption of *H. pustulata*, containing photosensitizing anthraquinones like rubiadin, can lead to primary photosensitization in animals, causing dermatitis and vision impairment. Rubiadin, classified as a Type I or Type II photosensitizer, induces similar reactions when orally administered to test animals.[112] It is recommended to administer soranjidiol and rubiadin 24 to 72 hours after consuming *H. pustulata* to align with clinical symptoms. Further research is needed to explore their toxicological effects and potential in photodynamic therapy, including reversing drug resistance.[113,114] Rubiadin's diverse effects on cancer cells highlight the need for further research to fully assess its potential and limitations in photodynamic therapy.

7 Future avenues

A review on rubiadin highlights its potential as a natural anti-cancer agent, recommending further research into combination therapies, targeted delivery methods, and molecular mechanisms. It emphasizes the importance of clinical trials across diverse populations, bioinformatics for biomarker discovery, and the development of modified analogues to enhance efficacy and safety.

8 CONCLUSION

To sum up, rubiadin's has potential as a natural anti-cancer agent. The analysis highlights rubiadin's intriguing role in cancer treatment, from its chemical structure and various sources to thorough insights into pharmacokinetics, molecular mechanisms, and practical factors. This in-depth analysis makes a strong argument for more research by highlighting the many facets of rubiadin and its potential to be an important player in the quest for novel cancer treatments.

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