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REVIEW OPEN ACCESS

Investigating Therapeutic Potential of Targeting Platelets in Cancer Treatment: A Literature Review

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Abstract

Cancer is one of the leading causes of global mortality and continues to persist as a significant healthcare burden. Patient non-responsiveness or relapse following first-line cancer treatments necessitates the development of novel treatments. Platelets are small blood cells that are essential to stop bleeding. Platelets are increasingly recognized for their roles in supporting tumorigenesis. They can aid cancer cells to evade immune cells, promote immune suppression, and release molecules that protect the stability of tumor microenvironments. Conversely, platelets can also secrete molecules that recruit leukocytes to the site of tissue injury and coordinate immune cell responses and crosstalk. Anti-platelet therapies, including aspirin, have been advocated as preventive measures in some cancers, but the long-term risks for bleeding, thrombotic events, ineffective immune responses, and overall efficacy towards cancer recovery remain uncertain. To address these gaps, this literature review reports pre-clinical studies and clinical trials from 2017-2023 that explore (1) novel molecules and pathways participating in platelet and cancer cell crosstalk, (2) overall efficacy of cancer treatment or effects on cancer cell survival, proliferation, and metastasis, and (3) safety of anti-platelet therapy. This study's findings reveal that anti-platelet therapies have an improved benefit for the prevention and treatment of some cancers, such as colorectal, breast, prostate, or lung cancers. There has been some success using anti-platelet treatments, such as ticagrelor to inhibit P2Y12 pathway, or low molecular weight heparin. While aspirin usage was successful in some cancers, such as colorectal cancer, it was not effective in others, such as ovarian cancer. Finally, the safety of using anti-platelet medications was explored; these medications may increase the risk of bleeding and other side effects, even if they have demonstrated promise in lowering the risk of cancer and increasing patient survival. Overall, this review highlights the complex interactions between platelets and different cancers, with considerations for cancer treatment efficacy and safety.

Keywords: platelets; cancer; tumor; metastasis; tumorigenesis; therapeutic target; aspirin

Introduction

One in six fatalities worldwide are attributed to cancer. In 2020, the global incidence of cancer was 19.3 million cases, while approximately 10 million lives were lost [1]. With no universal cure available, cancer continues to prevail as a formidable public health care challenge [1,2]. While traditional first-line treatments, such as surgery, chemotherapy, and radiation, have extended the survival rates of many cancer patients, a substantial fraction may be nonresponsive or relapse in later stages of disease. This necessitates the development of novel cancer therapies [1].

Platelets – Friend or Foe of Cancer?

Platelets are small blood cells that are appreciated for their critical roles to stop bleeding. However, they exhibit many diverse functions, such as modulating immune cell activation and behaviour and aiding in tissue repair, organ development, and angiogenesis [3]. Platelets are increasingly being recognized for their roles in promoting tumorigenesis and metastasis. They may adhere directly to cancer cells, forming platelet-cancer aggregates, which can shield the cancer cells from immune cell detection [4]. This strategy is particularly useful during cancer metastasis; platelets can form a "cloak" around circulating tumor cells (CTCs), which are cancer cells that have detached from the primary tumor and have entered the bloodstream. This not only protects the CTCs from immune surveillance, but also the shear forces in the bloodstream [5]. Platelets can also transfer their surface receptors to cancer cells, which helps the cancer cells evade recognition by the immune system [6].

Moreover, platelets release various signaling molecules and factors that may hinder immune cell activity and capacity to recognize, while also supporting tumor growth [7]. For instance, in the tumor microenvironment (TME), platelets may release transforming growth factor beta (TGF-β), which can downregulate a key receptor on natural killer (NK) cells involved in cancer cell recognition and destruction [7]. Platelets can also release pro-angiogenic

factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which helps to form new blood vessels that can deliver additional nutrients to the TME [8].

Conversely, platelets possess immune cell-like behaviour. They express toll-like receptors (TLR), such as TLR2, which helps to sense and eradicate pathogens [9]. Platelets can release molecules such as cluster of differentiation (CD) 62P and CD40L that recruit leukocytes into inflamed tissues and enhances T and B cell activation and crosstalk [10]. These strategies may be important in assisting the immune system to control and/or eliminate cancer cells. As such, investigating the multifaceted relationships between platelets and cancer cells is an important avenue of cancer therapy [11].

Current Strategies Targeting Platelets in Cancer Therapy

Acetylsalicyclic acid (ASA), otherwise commonly known as aspirin, has "anti-platelet" functions and is considered the gold standard medication to treat arterial thrombosis [12]. It works by acetylating the amino acid serine at position 529 of the enzyme cyclooxygenase (COX). This blocks the substrate, arachidonic acid's, access to the catalytic site of COX, thereby irreversibly suppressing platelet-dependent thromboxane production and platelet activity. Due to its recent success in clinical trials, aspirin has been recommended as a chemopreventive medication in colorectal cancer (CRC) by the U.S. Preventive Services Task Force [13].

The use of aspirin risks impairing normal platelet hemostatic function. As such, its use is targeted towards populations with risk factors for cardiovascular disease (CVD) and CRC but need not be formally diagnosed in either or both [14]. Typically, individuals prescribed aspirin for CRC are adults 50–59 years old with at least 10% risk of developing CVD over a period of 10 years. They must not have any other comorbidities that increase their bleeding risks. These guidelines and recommendations were based on the CRC patient characteristics in the cohorts examined in the clinical trials, however, may adjust depending on specific requirements of each patient [14].

A meta-analysis conducted by Rothwell et al. demonstrated a consistent link between regular aspirin intake and a decreased risk of colon cancer. Participants in four randomised trials of primary and secondary prevention of vascular events were divided into two groups: aspirin vs control. According to the study, aspirin, at any dosage, decreased the long-term risk of colon cancer but not rectal cancer throughout the duration of a mean 5.8-year course of treatment. Proximal colon cancers, which cannot be effectively prevented by screening with sigmoidoscopy or colonoscopy, benefited the most from the reduction in colon cancer risk in participants whose trial treatment was intended to last for five years or more [15]. However, the current understanding of whether the use of aspirin is effective in other cancers is still limited. In a clinical trial reported by Elwood et al., they discovered that using aspirin increased prostate and breast cancer patient survival and decreased instances of recurrence. The use of low-dose aspirin decreased the incidences of distant metastasis in colorectal cancer (CRC). Despite these promising findings, more randomised, placebo-controlled clinical trials investigating the efficacy of aspirin therapy on other cancers are warranted [16].

Potential Risks of Targeting Platelets in Cancer Therapy

Anti-platelet therapies may pose risks for excessive platelet activation leading to thrombotic events [17]. This would be especially detrimental if used as a treatment for pancreatic, stomach, lung, ovarian, and brain cancer patients, as thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), and other venous thromboembolism (VTE) events have already been reported [18]. Moreover, a higher frequency of prothrombotic conditions have been detected in metastatic and advanced cancers [19]. Therefore, in addition to patient-specific considerations, the type and stage of cancer and associated thrombotic risks should be considered prior to anti-platelet therapy [19].

Thrombin activation of platelets through protease-activated receptors (PARs) stimulates the release of soluble mediators, which may promote tumor development, angiogenesis, and metastasis. Notably, these thrombin-responsive receptors are expressed on a variety of other cells, such as endothelial cells, leukocytes, and cancer cells [20]. Therefore, a potential approach for anti-platelet cancer treatment has been to target the thrombin-PAR axis by either directly inhibiting thrombin or blocking the activation of PARs. This mechanism primarily aims to reduce the pro-tumorigenic activity of platelets in the TME and may assist in slowing the evolution and spread of cancer [19]. However, it is unclear how the thrombin-PAR axis would be affected in these other PAR-expressing cell types, whether that would be detrimental for physiological functions, and how to avoid or minimize these off-targets.

Moreover, some cancer patients, particularly those with breast, ovarian, and lung cancers, tend to have elevated platelet counts [20]. This may increase susceptibility to thrombotic events. A review article by Xu et al., indicated that high platelet counts may be controlled by restricting thrombocytosis and modifying platelet development pathways [20]. Whether these anti-platelet therapies could be used in combination with traditional cancer therapies to regulate platelet numbers is unknown.

Alternatively, some anti-platelet therapies might impair platelet function or cause depletion, resulting in increased and/or prolonged bleeding events. As previously described, aspirin is an example of an anti-platelet therapy that reduces platelet function. While aspirin use was beneficial in treating certain cancers, it also places certain individuals at higher risk of bleeding [21]. Thrombocytopenia, a condition defined by low platelet counts, can result from particular medications

or therapies, such as radiation therapy or chemotherapy used in cancer treatment. Thrombopoietin (TPO) is a hormone that is the primary regulator of platelet production and, therefore, platelet numbers. Mechanistically, TPO works by binding to its cognate receptor on the surface of megakaryocytes, stimulating thrombopoiesis. TPO receptor agonists, such as eltrombopag and romiplostim, are currently approved drugs for chronic immune thrombocytopenia (ITP) patients. They aim to increase platelet production, lower bleeding incidents, and reduce the requirements for rescue or supplementary medication. TPO receptor agonists may be used alongside typical cancer treatments in those patients with a risk for bleeding [21].

As platelet-immune cell crosstalk may promote or suppress immune cell activity, it is unknown how using anti-platelet therapies would affect the cancer patient's immune system activation and efficacy. Whether utilizing anti-platelet treatments in conjunction with other immunomodulatory agents (e.g. chimeric antigen receptor T cell and NK cell therapy) may synergistically reduce tumor burden and spread is unclear. Therefore, comprehending the intricate interplay between platelets, cancer cells, and immune cells is imperative to harness the full potential of anti-platelet therapies [17].

There is a gap in knowledge regarding whether targeting platelets and their molecules are beneficial or harmful for cancer recovery. Therefore, the objective of this study is to summarize recent pre-clinical studies and clinical trials targeting platelets to treat cancer [22].

This study intended to assess the therapeutic potential of targeting platelets in cancer therapy. The research methodology involves a comprehensive review of pre-clinical studies to investigate the function of platelets in cancer development and treatment effectiveness. The findings of this study, contain the potential to have an impact on the current therapeutic treatments while opening possibilities for more effective cancer therapies.

Methods

To conduct this study, a search of the PubMed database was performed using specific keywords such as "cancer", "platelets", and "aspirin." The search was initially restricted to clinical trials published between January 2017 and December 2023 (Table 1). According to Figure 1, as limited clinical trials for anti-platelet therapies used in cancer were found within this period, the search expanded to include pre-clinical studies. Keywords such as "animal study" and "in vitro" were added to the PubMed search to differentiate pre-clinical studies from clinical trials.

Table 1. Study Selection Criteria

Database	Search Terms	Inclusion Criteria	Data Range
PubMed	"Cancer", "platelets", "aspirin"	Clinical trials, pre-clinical studies, English language	January 2017-December 2023

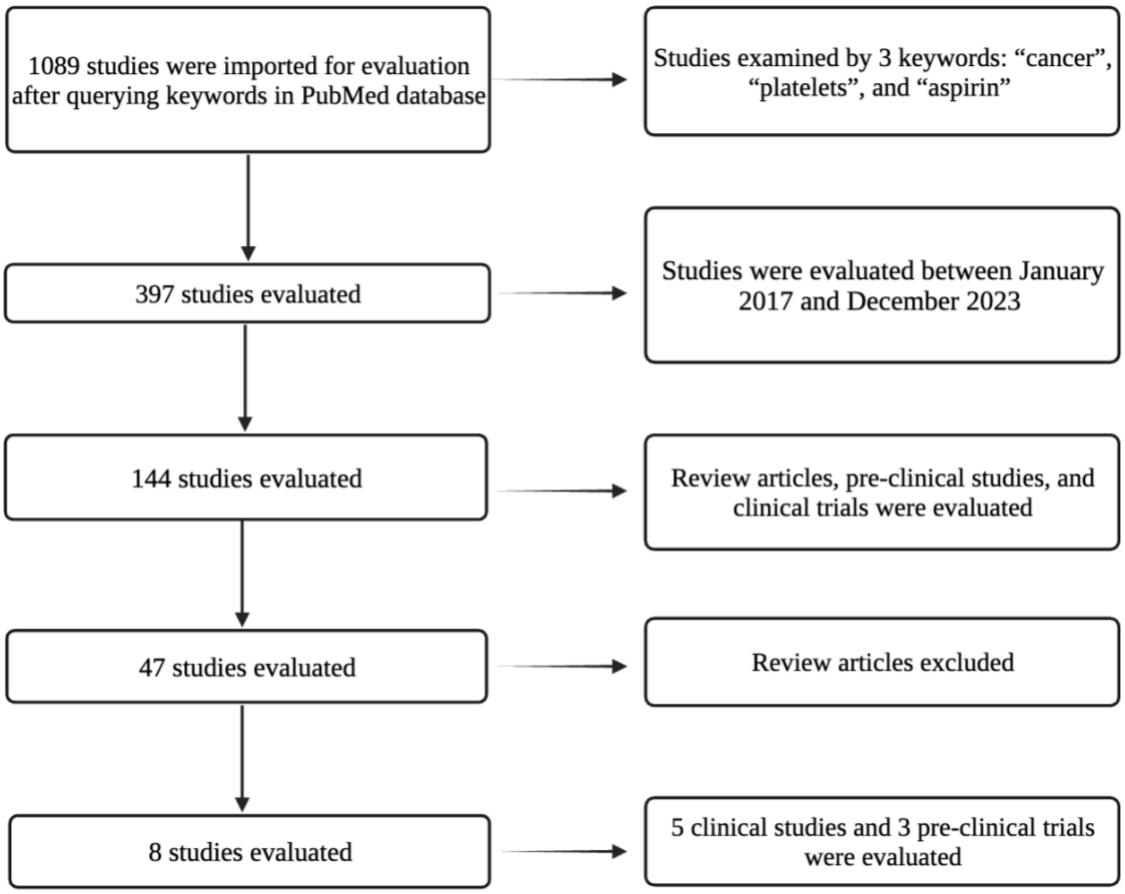

Figure 1. Flowchart of Data Extraction from Pubmed.com (created with Microsoft Word).

Results

The pre-clinical studies comprised of chronic myeloid leukaemia (CML), ovarian cancer, and breast cancer (Table 2). Pre-clinical studies investigated how anti-angiogenic treatments affected platelet-tumor cell interaction. Most clinical trials in this review were found to be in phases 1 and 2, and they encompassed gastric cancer, breast cancer, and non-small cell lung cancer (NSCLC). Table 3 provides details about the clinical trials which examined the safety and effectiveness of thrombopoietin receptor (TPO-R) agonists and anti-programmed cell death (PD)-1 therapy in combination with chemotherapy and anti-angiogenic treatments.

Table 2. An overview of the pre-clinical studies examined

		Pre-Clinical Studies			
Author and Year [Ref]	**Animal Model/Cell Line**	**Platelet Molecules and Pathways Targeted**	**Type of Cancer**	**Anti-Platelet Drug**	**Main Findings**
Johnson et al., 2019 [9]	Human breast cancer cell lines (MCF-7, MDA-MB-231, BT-20, and SKBR-3)	Akt pathway in breast tumor cells	Breast cancer	Aspirin	Aspirin treatment lowered tumor cell interleukin (IL)-8 release, platelet activation, and the metastatic phenotype of breast tumor cells.
Haemmerle et al., 2016 [22]	C57BL/6 mice were orthotopically injected with a murine ovarian cancer cell line (ID8-VEGF).	Platelet-derived growth factor (PDGF), platelet factor 4 (PF4), focal adhesion kinase (FAK), vascular endothelial growth factor (VEGF), adenosine diphosphate (ADP)-receptor antagonists 12	Human and mouse ovarian cancer cells (HeyA8, SKOV3ip1, OVCAR5, A2780, and 2774)	Monoclonal anti-glycoprotein Ibα (GPIbα) antibody	Platelet infiltration into the tumor microenvironment led to tumor growth following cessation of anti-angiogenic therapy. Platelet extravasation was important to promote tumor growth.
Gareau et al.,2018[23]	Adult female BALB/c mice, human mammary carcinoma cell lines (MCF-7, MDA-MB-468, and MDA-MB-231), human myelogenous leukemia cell line (K562), mouse mammary carcinoma cell line (4T1)	Purinergic receptor P2Y12 on platelets	Breast cancer	Ticagrelor & the irreversible thienopyridine P2Y12 inhibitor clopidogrel	Anti-platelet drug ticagrelor effectively reduced platelet release of P-selectin and interaction with P-selectin glycoprotein ligand-1 (PSGL-1) on breast cancer cells. Ticagrelor did not affect proliferation of cancer cells or primary tumor growth in mice.

Table 3. An overview of the clinical trials examined

Study Type		**Clinical Trials**				
Author and Year [Ref]	**Patient Characteristics (Age, Sex, Medications)**	**Participants (n)**	**Platelet Molecules and Pathways**	**Type of Cancer**	**Anti-Platelet Drug**	**Main Findings**
Kilvaer et al., 2019 [24]	Median age: 67 (age range: 28-85), patients' smoking status, surgical procedures, adjuvant radiotherapy, differentiation degree of differentiation of the tumor cells, pStage (the pathological stage), tStage (the clinical stage), nStage (the stage of the cancer based on if it has spread to nearby lymph nodes).	553	Platelet-derived growth factor receptors (PDGFRs)	Non-small cell lung cancer (NSCLC)	Cediranib	PDGFR isoform expressions distinctly predicts NSCLC patient survival in a stage- and histotype-specific path, emphasizing the possible significance of PDGFRs in cancer prognosis.
Liu et al., 2020 [25]	211 males, 494 females, mean age: 45.02 (age range: 33.56-56.48)	705	Platelet-derived growth factor (PDGF)	Papillary thyroid cancer (PTC)	N/A	Decreased platelet counts pre-treatment might be an indication of a poor prognosis in PTC.
Riedl et al., 2017 [26]	62 cancer patients and 30 healthy controls. Median age for cancer patients: 63 (age range: 54-70) and median age for healthy controls: 53 (age range: 50-61). 48.4% of cancer patients were female. 72.6% of cancer patients had stage IV cancer	92	Protease-activated receptors (PARs), integrin αIIbβ3 monocyte-platelet aggregates (MPAs), soluble P-selectin	Lung, pancreas, brain, colon, and stomach cancers	Aspirin	Lower platelet reactivity upon agonist-induced activation ex vivo was correlated to higher mortality rates and an increased risk of VTE in cancer patients. All cancer patients were associated with an elevated risk of VTE.
Wu et al.,2023 [27]	58.2% were <65 years old and 41.8% were ≥65 years old. 84.2% of patients were men and 15.8% were women. All cancer patients were undergoing	271	Patients with NSCLC who received first-line anti-PD-1 therapy with chemotherapy, which included pemetrexed + cisplatinum/carbopla	Advanced NSCLC	Bevacizumab	Platelet to lymphocyte ratio (PLR) ≥200 was associated with to worse overall survival (OS) and progression-free survival (PFS). Lower immunotherapy

Study Type		**Clinical Trials**				
Author and Year [Ref]	**Patient Characteristics (Age, Sex, Medications)**	**Participants (n)**	**Platelet Molecules and Pathways**	**Type of Cancer**	**Anti-Platelet Drug**	**Main Findings**
	chemotherapy in addition to anti-PD-1 treatment, either in combination with or without anti-angiogenic treatment		tin and paclitaxel + cisplatinum/carboplatin. Some patients also acquired anti-angiogenic agents, including bevacizumab and endostar. All patients acquired at least 2 cycles of anti-PD-1 and chemotherapy.			efficacy may be associated with higher PLR.
Xing et al., 2019 [28]	Median age: 51 (age range: 30-73). 15 patients had estrogen receptor or progesterone receptor -positive disease, 3 had HER2-positive disease, 9 had triple-negative breast cancer, 4 had previously received everolimus, a drug that blocks the mammalian target of rapamycin (mTOR) pathway and is used to treat diverse types of cancer	27	PAKT, platelet activation markersPI3K/AKT/mTOR signaling	Advanced breast cancer	N/A	Platelet activation was significantly reduced after treatment with MK-2206 (an inhibitor of PI3K/AKT/mTOR signaling pathway) dose-dependent reduction in tumor development occurred after receiving MK-2206 therapy.

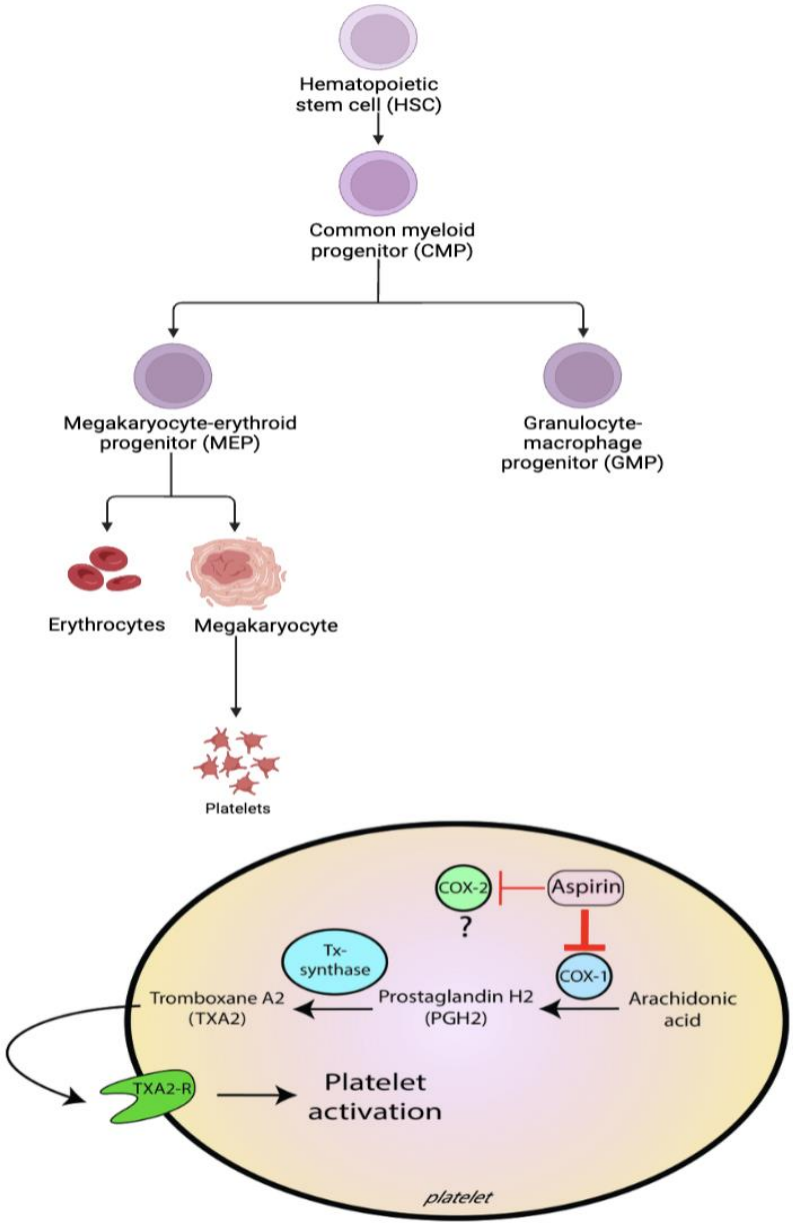

Figure 2. Platelet formation and Aspirin's target in platelets [29]. Created with Biorender.com

Discussion

Platelets and platelet-derived factors may contribute to the progression, spread, and resistance of cancer. This review examines whether aspirin and other anti-platelet agents have efficacy against several types of cancer, describes the pathways and molecules that are targeted, and overall safety.

Novel Strategies for Targeting Platelets to TME

For individuals with normal platelet counts, blocking platelet activation could be a beneficial treatment, but it is probably not the most effective treatment for thrombocytopenic patients (i.e., <150 x 10^9 platelets/L). This is due to the potential for impaired platelet hemostatic function, which may result in bleeding problems. Delivering platelet inhibitors directly to the tumor microenvironment might effectively prevent tumor growth and metastasis while minimizing hemostatic problems. Moreover, in a mammary cancer mouse model, tumor homing liposomal nanoparticles containing the anti-platelet inhibitor, ticagrelor, effectively targeted tumor-associated platelets and significantly decreased lung metastases. Using nanoparticle-mediated delivery of siRNA to the metastasis site presents an opportunity to target and silence tissue factor (TF) overexpression in cancer cells, which may decrease metastases [17].

Benefits of Aspirin Therapy for Breast Cancer

Further study is needed to understand aspirin's efficacy and mechanisms of action as a chemo-preventive drug. Daily low-dose aspirin prescribed for cancer patients may lower the chance of cancer cell survival, spread, and the long-term risk of cancer-related mortality [14]. According to an in vitro study using breast tumor cell lines, platelet activation, and granule release can promote the metastatic phenotype of breast tumor cells through upregulated Akt signaling and IL-8 secretion by tumor cells. Aspirin therapy reduced platelet activation, tumor cell IL-8 secretion, and metastatic potential of breast tumor cells [9]. Significant reductions in mortality were observed in breast cancer patients who have taken aspirin daily. patients with breast cancer receiving aspirin had on average, a 14.17 ng/mL decrease in circulating CCL5 and a 5.47 pg/mL decrease in circulating IL-8 compared to patients not receiving aspirin as reported by Johnson et al [9]. A long-term epidemiological study by Rothwell et al. showed that taking aspirin daily for several years at doses of at least 75 mg, reduced the long-term incidence of colorectal cancer by 24% and mortality due to colorectal cancer by 35% over a 20-year period. Furthermore, the reduction in the risk of death due to colorectal cancer was higher than the reduction in incidence. These findings suggest a significant improvement in both the incidence and mortality rates of colorectal cancer among individuals taking aspirin daily [15]. In particular, women who used aspirin on a regular basis showed a significant decrease in mortality from breast cancer [30]. However, more studies are required to fully understand the possible advantages of aspirin therapy in the treatment and recovery of cancer. It is also essential to take into consideration the risks and adverse reactions of aspirin, mainly when using it excessively or in high dosages [9].

Targeting P2Y12 and PAR-1 Pathways in Anti-Platelet Cancer Therapy

The exact roles of platelets at various stages of cancer and signaling pathways involved in their pro- and anti-tumor activities are still being clarified. However, platelet inhibition by prasugrel ticagrelor, or vorapaxar, in addition to aspirin, correlated with reduced tumor growth and decreased cancer-associated death in several clinical trials [20]. P2Y12 receptor antagonists such as ticagrelor and prasugrel effectively inhibited platelet activation and aggregation. Conversely, vorapaxar, an antagonist of PAR-1, prevented thrombin-induced platelet activation. Activation and aggregation constitute two sequential steps of platelet functions that may be targeted. This may be a preferred approach to simply decreasing the platelet count [20]. Palacios-Acedo et al. demonstrated in an animal model of pancreatic cancer that treatment with the P2RY12 antagonist clopidogrel decreased the size of pancreatic tumors and decreased incidences of metastasis [31].

Targeting P2Y12 and ADP Pathways in Ovarian Cancer

CD39 is an enzyme expressed on the surface of leukocytes, platelets, and endothelial cells. Cho et al. discovered that CD39 regulates purinergic signaling, which influences platelet reactivity and tumor growth. In the presence of platelets, P2Y12 inhibition reduced platelet-enhanced cancer cell proliferation, while knockdown of CD39 increased it. These results suggest that P2Y12 on platelets and ADP concentration play a crucial role in the interaction between platelets and ovarian cancer cells. Targeting P2Y12 may be a potential therapeutic option for ovarian cancer treatment [32]. However, the success rate would vary depending on the type of cancer and genetic background of the patient. Notably, these conclusions were obtained from pre-clinical studies in mice; further clinical trials are needed to confirm their findings [32].

Targeting Pathways and Molecules to Inhibit Cancer Metastasis

Platelets can facilitate tumor arrest at the endothelium, extravasation, and seeding. The contribution of platelets to tumor arrest at the endothelium involves adhesive interactions between platelets and endothelium, tumor cells, and leukocytes. In addition to “platelet cloaking,” platelets can rapidly associate with metastatic tumor cells via their receptors and cause tumor cell-induced platelet aggregation (TCIPA) in circulation [20]. Some of the molecules involved in these interactions include platelet integrin αIIβ3, which typically binds to fibrin(ogen) or fibrin–fibronectin complexes but may also bridge tumor αVβ3. Platelet integrin α6β1 may also bind ADAM9 on tumor cells to enhance platelet activation and tumor cell extravasation [20].

Multiple studies have highlighted concerns regarding the possibility of rebound tumor development, hypoxia induction, and metastatic facilitation following anti-angiogenic medication discontinuation. Clinical trials using anti-angiogenic medications and chemotherapy demonstrated that the duration of the anti-angiogenic drug bevacizumab treatment has a direct correlation with its effects on survival. The progression-free survival curves tended to collapse or even cross over once the anti-angiogenesis medication was discontinued. The anti-angiogenic treatment reduced the growth of primary tumors in preclinical models, but for unknown reasons, it also enhanced the propensity for tumors to spread. Furthermore, it was demonstrated that anti-angiogenic medication caused considerable hypoxia, which could assist in metastasis [22].

The Potential of Using TPO in Anti-Cancer Therapy

Patients receiving cancer therapy might be more probable to develop bleeding if they have thrombocytopenia. TPO receptor agonists, such as romiplostim and eltrombopag, have been demonstrated to effectively increase platelet counts in thrombocytopenic patients. For cancer patients after chemotherapy, increasing platelet counts may help avoid bleeding problems. However, there are some

risks associated with their usage; TPO receptor agonists may trigger headache, fatigue, arthralgias, nausea, and nasopharyngitis as side effects. Furthermore, the use of TPO receptor agonists has been linked to reports of thromboembolic events and bone marrow fibrosis [22]. Interestingly, individuals diagnosed with ITP may be more prone to certain cancers, including lymphoproliferative diseases and chronic lymphocytic leukaemia. However, further research must be conducted to determine the mechanisms and the factors that contribute to it [21].

Safety of Anti-Platelet Drugs Against Bleeding and Thrombotic Events

Anti-platelet medication, in particular dual anti-platelet therapy (DAPT), was shown to worsen prognosis in cases of bleeding, resulting in higher mortality rates, in comparison to aspirin monotherapy or no anti-platelet therapy. DAPT is the term for the combined use of two anti-platelet drugs, most frequently aspirin and a P2Y12 inhibitor such as ticagrelor, prasugrel, or clopidogrel. To avoid stent thrombosis and associated cardiovascular events, this combination is frequently administered to patients who have had an acute coronary syndrome or who have had coronary stent placement [33]. It is essential to remember that the safety of the anti-platelet medications against thrombotic and bleeding events might change based on the patient's individual characteristics and the specific clinical setting in which they are being treated. Several options for treatment, such as reversal of anti-thrombotic medication, might be taken into consideration to control bleeding events related to anti-platelet therapy. Meanwhile, platelet transfusion is still one of the main techniques used to mitigate the effects of anti-platelet therapies on primary hemostasis. In contrast to anti-platelet therapy, platelet transfusions may have different concerns and implications when employed for the treatment of cancer. While platelet transfusions are used to increase the platelet count and stop or prevent bleeding in cancer patients, there is still more to discover and discuss on how effectively platelet transfusion might reduce the negative effects of anti-platelet medications on primary hemostasis [33].

Potential and Challenges of Anticoagulants for Cancer Therapy

Many cancer patients are already using anticoagulant or anti-platelet therapies, such as direct oral anticoagulants (DOACs), low molecular weight heparin (LMWH), warfarin (a vitamin K antagonist), and anti-platelet drugs such as clopidogrel or aspirin [36] because of other medical conditions including atrial fibrillation or ischemic attacks. By inhibiting platelet aggregation or clotting factors, these drugs lower the risk of blood clots. Therefore, managing the anticoagulant and anti-platelet therapies in cancer patients presents difficulties for medical professionals in terms of diagnosis as well as treatment. In addition to continuously monitoring patients for bleeding issues, healthcare practitioners should carefully consider the benefits and challenges of anticoagulation in cancer patients [36].

Future Directions

While aspirin is the first anti-platelet drug approved for use in cancer treatment, clopidogrel, ticagrelor, prasugrel, pentoxifylline, cilostazol, and dipyridamole are other oral anti-platelet medications. Clopidogrel may have some anti-cancer benefits, especially in cases of colorectal cancer. Nevertheless, the evidence is limited, and further study is required to validate these conclusions [34,35]. Low molecular weight heparins (LMWHs) have been shown to inhibit platelet activation and aggregation, as well as reduce the release of pro-angiogenic factors, which may contribute to their anti-tumor effects [5].

Limitations of this Study

One notable challenge when conducting this study is the variability among the selected clinical trials and pre-clinical studies. For instance, it may be difficult to make generalisations from the literature due to the variety of approaches, patient demographics (e.g. age and sex variability), and cancer types that are included. Although clinical trials represented most of the information used in this study, the analysis was limited by the number of studies. The retrospective approach used in many clinical trials may include confounding factors and inherent biases, making it more difficult to determine a cause-and-effect link between the results of cancer treatment and platelet-targeted treatments. The lack of specific information on the availability of some data in this study, such as age and sex in some pre-clinical studies, may make it more challenging to reproduce and validate the authors' findings.

Conclusion

This literature review presents an up-to-date assessment of the benefits and risks of targeting platelets and their molecules for cancer therapy. Anti-platelet treatment for cancer therapy was found to be helpful for some types of cancer, such as pancreatic and ovarian cancers. The anti-platelet medication aspirin significantly reduced the risk of certain cancers, including breast, stomach, and colorectal cancers. Furthermore, anti-platelet drugs have been demonstrated to enhance cancer patients' prognoses, especially for those with lung, prostate, and colorectal cancer [7]. Despite these encouraging results, anti-platelet therapy for cancer treatment is still in its early phases of development [38]. Improving the understanding of the precise mechanisms by which platelets interact with types of cancer cells would be beneficial to further develop these therapies that can specifically decrease platelets' pro-tumor behaviours while maintaining their anti-tumor advantages. Given platelet's essential roles in hemostasis, a current challenge in developing anti-platelet therapies for cancer is the possibility of increased bleeding risk. Thus, from the results of this study, there is an emphasis on

carefully balancing the bleeding risks with the anti-tumor advantages of platelet inhibition.

List of Abbreviations Used
ADP: adenosine diphosphate
ASA: acetylsalicylic acid
CML: chronic myeloid leukemia
COX: cyclooxygenase
CTC: circulating tumor cell
CVD: cardiovascular disease
DAPT: dual anti-platelet therapy
DOAC: direct oral anticoagulant
DVT: deep vein thrombosis
FAK: focal adhesion kinase
FGF: fibroblast growth factor
IL: interleukin
ITP: immune thrombocytopenia
LMWH: low molecular weight heparin
MPA: monocyte-platelet aggregate
NK: natural killer
NSCLC: non-small cell lung cancer
PAR: protease-activated receptor
PD-1: programmed cell death protein 1
PDGF: platelet-derived growth factor
PDGFR: platelet-derived growth factor receptor
PE: pulmonary embolism
PF4: platelet factor 4
PLR: platelet-to-lymphocyte ratio
PTC: papillary thyroid cancer
PSGL: P-selectin glycoprotein ligand-1
SCC: squamous cell carcinoma
TCIPA: tumor cell-induced platelet aggregation
TGF-β: transforming growth factor beta
TKI: tyrosine kinase inhibitor
TLR: toll-like receptor
TME: tumor microenvironment
TPO: thrombopoietin
VEGF: vascular endothelial growth factor
VTE: venous thromboembolism

Conflicts of Interest
The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent
No ethics/ participant consent was needed to complete this study.

Authors' Contributions
BT: made contributions to the design of the study, collected, and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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