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Review

Re-Assessing the Role of Platelet Activating Factor and Its Inflammatory Signaling and Inhibitors in Cancer and Anti-Cancer Strategies

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Abstract

Since 2000s, we have outlined the multifaceted role of inflammation in several aspects of cancer, via specific inflammatory mediators, including the platelet activating factor (PAF) and PAF-receptor (PAFR) related signaling, which affect important inflammatory junctions and cellular interactions that are associated with tumor-related inflammatory manifestations. It is now well established that disease-related unresolved chronic inflammatory responses can promote carcinogenesis. At the same time, tumors themselves are able to promote their progression and metastasis, by triggering an inflammation-related vicious cycle, in which PAF and its signaling play crucial role(s), which usually conclude in tumor growth and angiogenesis. In parallel, new evidence suggests that PAF and its signaling also interact with several inflammation-related cancer treatments by inducing an antitumor immune response or, conversely, promoting tumor recurrence. Within this review article, the current knowledge and future perspectives of the implication of PAF and its signaling in all these important aspects of cancer are thoroughly re-assessed. The potential beneficial role of PAF-inhibitors and natural or synthetic modulators of PAF-metabolism against tumors, tumor progression and metastasis are evaluated. Emphasis is given to natural and synthetic molecules with dual anti-PAF and anti-cancer activities (Bio-DAPAC-tives), with proven evidence of their antitumor potency through clinical trials, as well as on metal-based anti-inflammatory mediators that constitute a new class of potent inhibitors. The way these compounds may promote anti-tumor effects and modulate the inflammatory cellular actions and immune responses is also discussed. Limitations and future perspectives on targeting of PAF, its metabolism and receptor, including PAF-related inflammatory signaling, as part(s) of anti-tumor strategies that involve inflammation and immune response(s) for an improved outcome, are also evaluated.

Keywords: inflammation; PAF; PAFR; PAF-inhibitors; cancer; metastasis; anti-inflammatory; anti-cancer; natural bioactives; metal-based anti-inflammatory mediators

1. Introduction

Albeit the promises of several anticancer approaches, cancer still remains one of the leading causes of death and a worldwide health concern [1–3]. Cancer encloses a broad spectrum of distinctive diseases hallmarked mainly by the abnormal and uncontrollable proliferation of cells that result in tumors [1,2]. A comprehensive insight into the various signaling pathways participating in all stages cancer formation, development and metastatic progression, is essential, for designing appropriate preventative and therapeutic strategies [3–6]. Most common cancer cases are known to affect human breasts, lungs, colon, rectum, skin and prostate [3,7]. Well-established cancer risk factors, including non-intrinsic, exogenous determinants such as radiation, viruses, chemical carcinogens and unhealthy lifestyle patterns like tobacco smoke, alcohol consumption, unhealthy dietary habits and physical inactivity [3,8–12], as well as endogenous risk factors (immune, hormonal, microbial, family-inherited cancer [13], DNA repair ability/inability, induced inflammation etc.) and intrinsic contributors (i.e., spontaneous errors in DNA replication), suggest some kind of causality but do not entirely account for cancer progression [1,7,11,12].

Evidently, cancer emerges from the buildup of numerous genetic mutations and inappropriate expression/non-expression of associated genes (tumor inducing and/or tumor suppressing genes), as a result of the reciprocal connection between individual genetic or behavioral factors, and hence, prompts abnormalities in the control of mainly cell division, multiplication, tumor angiogenesis, and prolifera-

tion, all of which are usually associated with inflammatory manifestations [1,3,5,14]. Inflammation is usually a normal response of our immune system against several insults, such as trauma and infections, but also against abnormal tumor formation and cancer. However, chronic inflammation increases the probability of cancer and enhances tumorigenesis and metastasis, by forming an inflammatory tumor microenvironment, that usually consists of engaged cancer, stromal and inflammatory cells [2,14].

Platelet-activating factor (PAF) [15] is the most potent lipid inflammatory mediator that is implicated in chronic inflammatory manifestations involved in chronic disorders, including tumor formation and progression, through an interplay of its signaling with several cancer-related inflammatory cytokines and chemokines [1,2]. A typical PAF molecule structure is generally known as 1-O-alkyl-2-acetyl-sn-glycero-3-phospho-choline [15], while other polar lipids and other molecules with similar structure and activity to those of PAF also exist. PAF and several PAF-like molecules are involved in many cancer-related pathological processes including angiogenesis, tumorigenesis and metastasis. A continuous inflammatory activation due to chronic or acute infections, environmental contributors, and lifestyle factors, is associated with the development of several cancer types, tumorigenesis, tumor growth and metastasis, with belligerent clinical features [16,17]. Chronic inflammation specifically, induces carcinogenesis via reactive oxygen and nitrogen species, cytokines, PAF and prostaglandins, leading to neoplastic transformation, cancer promotion, and recurrence even after therapy. Notably, tumor cells themselves can initiate and propagate such PAF-associated inflammatory conditions that will further promote tumor development, and neo-angiogenetic and metastatic procedures [1,2]. Therefore, systemic inflammation poses one of the predominant cancer-related mortality etiology [17,18].

Regardless of the defining factor of malignancy occurrence, treatment-wise approaches against cancer progression can generally be categorized into the following broad categories: chemotherapy, immunotherapy, radiotherapy, and surgery with targeted therapy, hormonal therapy, and cell therapy being lesser known but of equal importance—with their usage being sometimes interchangeable and even necessary for a more sought-after clinical outcome [19,20]. Surgery despite being hailed as the main curative treatment, isn't always enough. Therefore, the need for a wider scope of anti-cancer curative and palliative interventions in all stages of malignancy is evident [19,20].

Systemic Anti-Cancer Treatments (SACT), are represented by traditional chemotherapeutic cytotoxic agents further categorized as antimetabolites, DNA alkylators, DNA binders or cleavers, DNA topoisomerase inhibitors, and tubulin/microtubule inhibitors—the main mechanisms of the currently 80 cytotoxics that are heavily relied upon [21]. Immunotherapy and its biological agents as an adjuvant to chemotherapy, find application in both early and more advanced cases of cancer [22], and despite growing interest in further nano-enhancement towards selective cell-type metabolic inhibition [23], a clear survival benefit does not apply across the board [20,24–26]. Differences in therapy type bring about different toxicities. In addition, risk factors like age along with prognostic biomarkers, frameworks, and indexes, can elucidate potential limitations of patients, mainly when palliative care is discussed—a defining example being the comprehensive geriatric assessment (CGA) for older recipients of radiation oncology services [27].

The relationship between inflammation and cancer is integrated into the clinical setting through the realization and subsequent usage of inflammatory markers as prognostic tools [28]. In addition, nutritional factors may modify the relation of inflammation and cancer prognosis. For example, Nakamura *et al.* [22] showed that several inflammatory markers have a prognostic value only when the patient nutritional status is taken into account with the use of the Geriatric Nutritional Risk Index. The interaction between cancer-induced inflammatory responses and anti-cancer therapeutic agents, dichotomizes future plans of action, in which anti-PAF like drugs are used as an adjuvant to cancer treatment. For example, an increase in PAF-Receptor (PAFR) expression can benefit anti-cancer progression—via the pathway of Nuclear Factor kappa-B (NF-κB) induction, in cases such as melanoma, where the upregulated inflammatory molecules, including PAF, increase apoptosis in cancerous cells [1,2].

On the other hand, PAFR agonists, PAF and PAF-like ligands can help tumor survival through cell proliferation and anti-cancer treatment protection [29]. Subsequently, PAFR antagonists gather growing experimental interest as an adjuvant to anti-cancer treatments [29]. PAF as a mediator of inflammatory responses among other physiological processes, can be a focal point of re-assessing its remediation, alleviating and curative potential as an anti-cancer treatment area. In the initial stages of tumorigenesis and angiogenesis, PAF can pose as a focal point of the clinical prognosis. Since the induced by PAF inflammation and associated signaling are involved in several processes that take place within the tumor microenvironment, such as a tumor induced angiogenic activation of endothelial cells that usually leads to neo-angiogenesis, and therefore colonization of other tissues, it is apparent that an anti-PAF approach can provide benefits against these inflammation related tumor metastatic procedures [1,2].

da Silva Junior *et al.* [29] proved experimentally that remedies like chemotherapy and radiotherapy, induced excess production of PAF-like molecules and enhanced PAFR expression in the tumor microenvironment, while it was also discovered that PAF-antagonists reduced drastically tumor recurrence, and thus it was proposed that an assortment of chemo- and radiotherapy with PAF-antagonists, might

represent an encouraging approach for addressing cancer [29]. More recently, by observing PAF's way of generating and moving-utilizing bioactive extracellular vesicles, specifically microvesicle particles (MVPs), Travers *et al*. [30] revealed that pro-oxidative stressors produce oxidized PAF-antagonistic glycerol-phosphocholines, which in turn stimulate further enzymatic PAF production via PAFRs. As a result, MVPs formation and release were augmented, serving as a transmitting mechanism of PAF and similar bioactive agents and as potent PAFR antagonists [30].

Additionally, many inhibitors deriving from natural sources and especially dietary PAF inhibitors from the Mediterranean diet (MD), such as cereals, legumes, vegetables, fish, and wine, as well as MD micronutrients and extracts, could potentially hinder directly or indirectly, the pro-inflammatory activity of PAF—induced cancer [1,2,31]. Several bioactives found in MD foods, including polar lipids, phenolic compounds, carotenoids, terpenes, vitamins etc., favorably impact on all activity and metabolism of crucial inflammatory agents linked to chronic illnesses. These effects extend to PAF-related pathways, contributing to reduced inflammation, balanced homeostasis and lower risk of cancer and other inflammation-associated chronic health disorders [1,2,32].

In addition, several anti-PAF synthetic molecules have also been assessed for anti-cancer potential [2], while co-administration of potent PAF inhibitors improves remarkably the pharmacological action of cytotoxic compounds [33,34]. Therefore, the development of new compounds that display dual anticancer and anti-PAF activities can be considered as an interesting approach in the fight against cancer. Within this point of view, recent outcomes on the anti-PAF and anti-tumor potential of "metal-based inflammatory mediators" have surfaced within the last decade as potential anti-inflammatory, anti-platelet and anti-tumor pharmaceuticals [35].

Thus, apart from the multifaceted role of PAF in cancer, tumor metastasis and anti-cancer strategies, which since 2000s we have outlined, this article thoroughly reviewes natural and synthetic bioactive molecules, such as dietary bioactives and metal-based anti-inflammatory mediators, respectively, which possess dual anti-PAF and anti-cancer activities.

2. The Implication of PAF and Its Signaling on the Inflammation-Related Tumor Development, Progression and Metastasis

2.1 The Link of Inflammation, Tumorigeneses and Metastasis

Since the 19th century the German pathologist Virchow's suggested a correlation between inflammation and cancer, based on the simple observation that inflammatory cells are present in tumor biopsies. Epidemiological studies further confirm that chronic inflammation increases susceptibility to a plethora of cancer types [36,37]. Inflammation is the organism's way of protecting itself from exogenous and endogenous factors like trauma, microbial infections and toxic drugs [38]. Depending on the type of stimulus, a corresponding and well-defined pathological consequence takes place aiming to help the tissue return to its basal state. Tissue dysregulation caused by modern lifestyle characteristics constitutes para-inflammation, an adaptive response less serious than chronic inflammation, which changes the baseline homeostatic checkpoints [39]. Nevertheless, para-inflammation can end up to chronic inflammation, which is in turn implicated in several chronic disorders, including cancer and its metastatic procedures.

The presence of such stimuli and other risk factors can also unfavorably deregulate the control of cell division and cell death. In this case, an uncontrolled cell proliferation and apoptosis take place, which may conclude in cancerous conditions [40]. Risk factors that influence acquired (e.g., epigenetic changes or ultraviolet-induced mutations etc.) or existing predisposition factors (e.g., genes) are important for prevention and remediation. These risk factors usually induce inflammatory manifestations, which are further implicated in the formation of tumors. Inflammation broadly categorized as acute or chronic is a key homeostatic mechanism, that is considered as therapeutic or pathological, respectively [41]. Pathologically inflamed cells are under the upregulation of mediators like PAF which work in tandem with angiogenic factors to facilitate new blood vessel growth in existing malignancies [1,2,42]. Angiogenesis lays the groundwork for metastasis and is the last checkpoint before drastic changes occur in prognosis.

The multifaceted process of metastasis stands as the predominant cause of mortality among patients suffering from cancer. Over the decades, major breakthroughs in perceiving all molecular and cellular mechanisms underlying this fatal progression in cancer have been made. Nevertheless, the epithelial-mesenchymal transition (EMT) and plasticity (EMP) during cancer progression, as well as the exact stage of tumor development, where a primary tumor converts into a metastatic, are still inadequately comprehended [43,44]. Cancer metastasis, refers to the migration of cancerous cells—mainly via angiogenesis—to tissues and organs distant from the original tumor site, which in turn gives rise to new tumors (widely known as secondary and tertiary foci), thus, the induction of tumor formation in different body tissues [43,45–47]. The crucial process of angiogenesis is vital to cancer progression and metastasis.

Specifically, during the evolving metastatic process, healthy functioning cells transform into oncogenic ones that engage in activities such as uncontrollable multiplication, immune system evasion and resistance to natural cell death enhancement, while prompting new blood vessels' growth and tumorigenesis in remote organs, acquiring the ability to invade distant tissues and successfully surviving within the bloodstream [43,44]. As the mass of cancerous cells expands, the formation of neoplastic blood vessels during

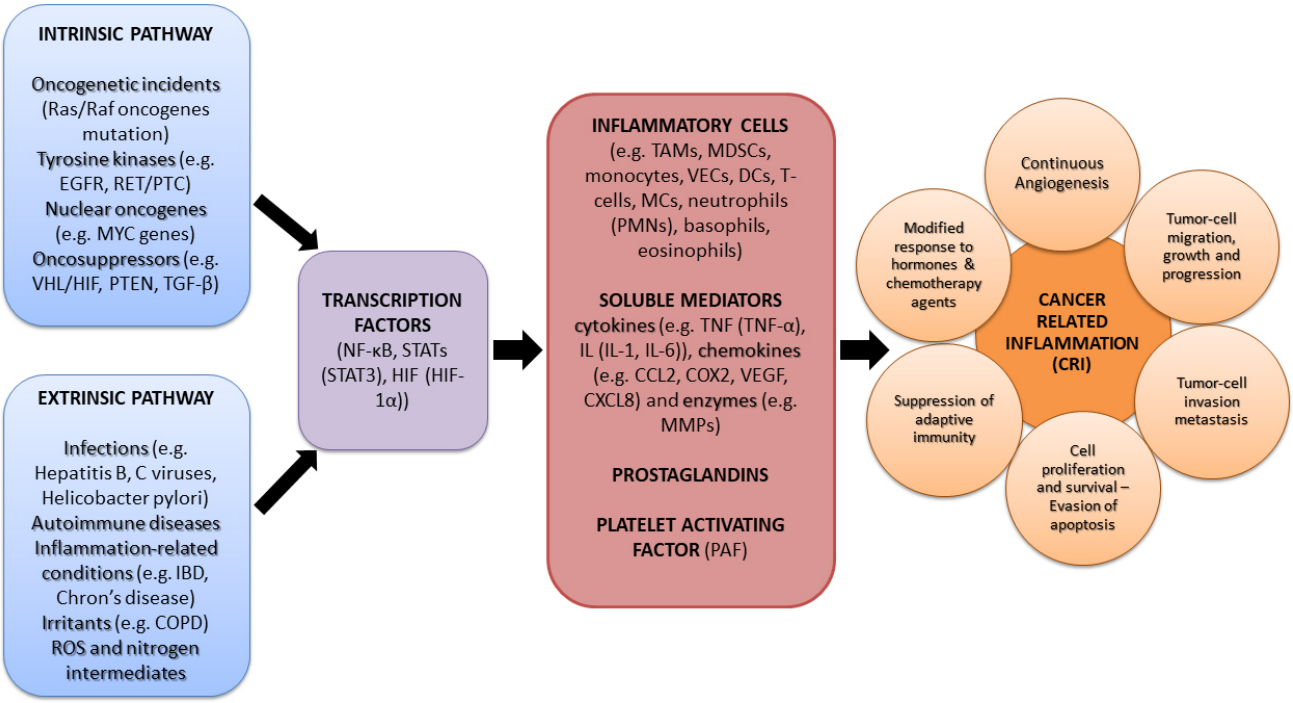


Fig. 1. Molecular pathways linking inflammation and cancer. Abbreviations: Ras/Raf, Rat sarcoma/Rapidly Accelerated Fibrosarcoma; EGFR, Epidermal Growth Factor Receptor; RET/PTC, Rearranged during Transformation/Papillary Thyroid Carcinoma; MYC, Myelocytomatosis; VHL/HIF, The von Hippel Lindau/Hypoxia-inducible Factor; PTEN, Phosphatase and tensin homolog; TGF-β, Transforming growth factor-β; IBD, Inflammatory bowel disease; COPD, Chronic obstructive pulmonary disease; ROS, Reactive oxygen Species; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3, Signal Transducer and Activator of Transcription 3; HIF-1α, Hypoxia-Inducible Factor 1-alpha; TAMs, Tumor Associated Macrophages; MDSCs, Myeloid-Derived Suppressor cells; VECs, Vascular Endothelial Cells; DCs, Dendritic Cells; MCs, Mast Cells; PMNs, Polymorphonuclear cells; TNF-α, Tumour Necrosis Factor alpha; IL, Interleukin; CCL2, chemokine (C-C motif) Ligand 2; COX2, Cyclooxygenase-2; VEGF, Vascular endothelial growth factor; CXCL8, chemokine (C-X-C motif) Ligand 8; MMPs, Matrix metalloproteinases.

angiogenesis ensure the provision of necessary oxygen and nutrients supply through blood stream, which further support tumor growth [2,48,49]. Moreover, cancerous cells may spread, invade and enter the bloodstream or lymphatic vessels, due to their direct induction of angiogenesis and thus, the creation of the acquired blood provision for secondary tumorigenesis [2,47–49]. The primary stages of cancer metastasis, are basically the formation of the primary tumor and cancer cells invasive dissemination, followed by the intravascular expedition and dormancy of newly formatted tumor cells in the bloodstream (Circulating Tumor Cells (CTCs)) and finally their extravasation and colonization in the tumor microenvironment [45,46,50,51].

Tumor-induced angiogenesis and neovascularization rely on multiple interactions among various cells, soluble substances, plus the extracellular matrix (ECM) constituents and involve four sequential stages. At first, the degradation of the basement membrane in the ECM as a result of the initiation of vessel activation [2,52]. In particular, cancer cells trigger the activation of endothelial cells (ECs) located on prior vessels, due to the fact that cancer cells' products/angiogenic factors, namely many cytokines and growth factors, strongly bind to their endothelium receptors, leading to said vessels' activation. By the time vessels are activated significant proteases (serine (SPs), matrix metallo-proteases (MMPs) etc.) which disintegrate the ECM, are excreted [2,46,49,52,53].

Subsequently, ECs participate in neovascularization, assemble their cytoskeleton, and express cell-surface adhesion molecules (integrins, selectins etc.). In parallel, ECs synthesize and discharge specific proteolytic enzymatic agents, so as to be able to re-establish later on the previously-decomposed ECM. Moreover, the colonization of cancer cells to healthy tissues is based on the cancer cells' attachment to neighboring interstitial cells and platelets enabled by specific adhesion molecules, the expression of which is favored by mediators secreted in the tumor microenvironment during neoangiogenesis [2,44,46]. As a consequence, the secondary and third angiogenesis phase, precisely the migration of ECs in the adjacent space and their resulting proliferation and stabilization respectively, occurs. Finally, the desired re-modelling of the ECM along with the significant lumen formation and formulated microvessels—maternal vessels interconnection take place, as the

fourth stage of angiogenesis [2,42,52,53]. The tumor induced and inflammation related processes of tumorigenesis, metastasis and angiogenesis, are intertwined and interdependent to ensure further tumor growth and colonization.

Tumor induced neo-angiogenesis is of great interest towards efficient anti-cancer strategies and therapies [2,54]. Anti-angiogenic therapies in conjunction with immune checkpoint inhibitors, may not always prevent cell spreading [44]. Thus, establishing the biological mechanisms behind cancer metastasis is of vital importance for future identification of hidden effective prospects for therapeutic interventions and maybe as a potential forthcoming stage of overall cancer metastasis comprehension [48,51].

Two are the primary molecular and cellular pathways connecting inflammation and cancer: the intrinsic and extrinsic one (Fig. 1). Considering the intrinsic pathways, many genetic alterations such as oncogenes drive the onset of inflammation-related processes [36,37]. In fact, intrinsic pathways connect inflammatory constituents located in tumors to oncogenes, showing that genetic incidences may cause neoplasia and initiate the inflammatory cascade. Main orchestrates and pro-inflammatory mediators participating in the intrinsic pathway of inflammation-related cancer, are oncogenes belonging to various molecular classes and operating modes. For example, tyrosine kinases like epidermal growth factor receptor (EGFR) [55] and the rearranged during transformation/papillary thyroid carcinoma (RET/PTC) [56] frequently induce human cancer. Moreover, among the various identified oncogenes, frequent mutations of the K - Rat sarcoma virus (*Ras*) gene, an isoform of the *Ras* gene for the Ras/Rapidly accelerated fibrosarcoma (Raf)/mitogen-activated protein kinase (MAPK) signal transduction pathway involved in cell cycle regulation, wound healing, tissue repair, integrin signaling, cell migration and angiogenesis, is directly involved in the formation of new blood vessels and tumorigenesis as well as high chemoresistance [44,57]. Nuclear oncogenes, like MYC tumor-linked genes, produce a transcription factor overly-expressed in tumors, the dysregulation of which initiates and sustains prime elements of the tumor phenotype, as well as immune evasion [58]. In addition, oncosuppressors including a plethora of tumor suppressor proteins (Hippel Lindau/hypoxia-inducible factor (VHL/HIF) [59], phosphatase and tensin homologue (PTEN) and the transforming growth factor-β (TGF-β) [60]), also facilitate several pro-inflammatory activities leading to angiogenesis and inflammatory tumor microenvironment formation, although further research is needed [36].

The extrinsic pathways are guided by inflammatory leukocytes and many soluble mediators [36,37]. In fact, infections associated with harmful pathogens such as human immunodeficiency virus (HIV), Hepatitis B and C viruses, Helicobacter pylori, etc. have been associated with several types of cancer [61,62]. Other inflammation-related disorders, such as autoimmune disease like Chron's disease [37], which mainly increase the risk of colorectal cancer occurrence, Inflammatory Bowel Disease (IBD) [63], metabolic syndrome and diabetes, chronic inflammatory pulmonary disorders, as well as a constant exposure to mechanical, radiation or chemical irritants [64], are proven as some of the leading extrinsic factors promoting tumor induction and progression [36,37]. Moreover, inflammation-related reactive oxygen species (ROS) and nitrogen intermediates, have been proven *in-vitro* and *in-vivo* to be responsible for DNA damage, implicated in abnormal cancerous cell proliferation [36,65]. On the contrary, anti-inflammatory and antioxidant bioactives, either of natural origin or synthetic ones, have been found to beneficially down regulate such manifestations [32].

The intrinsic and extrinsic pathways at some point converge as they induce transcription factors like the NF-κB, Signal Transducers and Activators of Transcription (STATs) and especially (STAT3), along with Hypoxia-Inducible Factors (HIF mostly the HIF-1α factor). These factors coordinate the formation of inflammatory mediators and the stimulation of different white blood cells—leukocytes, leading to an inflammatory and hence cancer-linked environment [36,66–70].

More particularly, all key-orchestrators mentioned above, organize the production of inflammatory cells (e.g., Tumor Associated Macrophages (TAM) [71], Myeloid-Derived Suppressor Cells (MDSC) [72], monocytes, vascular endothelial cells (VECs), dendritic cells (DCs), T-cells, mast cells (MCs), neutrophils including polymorphonuclear cells (PMNs) [49], as well as basophils, eosinophils etc.), as well as specific soluble mediators including growth factors, cytokines and chemokines present in the tumor micro-environment, which even though are initially expressed as a normal response to controlled apoptosis and pyroptosis, they can activate undesirable cell proliferation [39]. Interestingly, PAF is a junction mediator of such intracellular and intercellular messaging [1,2], even between other signaling compounds [73] and acts mainly in a juxtracrine, but also in an endocrine and paracrine way [74], and thus it has also been characterized as an hormone and/or a cytokine.

2.2 PAF's Physiology and Involvement in Cancer and Tumor Metastasis

2.2.1 Inflammatory Manifestations and the Roles of PAF-Metabolism, PAF-Lile Molecules and PAF-Receptor Associated Signaling

PAF physiological and pathophysiological roles are tightly associated with the inflammatory responses induced by an initial stimuli, as well as with several thromo-inflammatory manifestations linked to a dysregulation of inflammation due to several reasons, including ancer-induced inflammatory response [2,32]. Usually, in the presence of an insult like a trauma and/or an infectious agent, homeostasis is disrupted and an inflammatory response is

induced to counterattack an insult. Then, the initial inflammatory stimuli for probing an homeostatic inflammatory response against this insult, usually involves also an induction of PAF-synthesis, among other inflammatory signaling, so that the acutely increased PAF-levels further instigate the initial signal for inflammation-related response and counterback of the insult.

PAF and its PAF-like homologous lipid molecules are specific, structurally defined ligands that exclusively bind and induce their biological activities through a unique seven-transmembrane G-protein-coupled receptor known as the PAF-receptor (PAFR) with exceptionally high affinity. The PAFR is expressed on the surface of various mammalian cells, such as leukocytes, neutrophils, platelets, macrophages, and endothelial cells. Binding of PAF and/or PAF-like lipids on PAFR triggers an assortment of intracellular signalling cascades that can also result in further induction of PAF-synthesis and the expression of genes for inflammatory enzymes, mediators, chemokines and cytokines and their associated receptors, including PAFR itself [32,75,76]. This action is followed by a subsequent initiation and/or amplification of the inflammatory processes, including those involved in the initiation and progression of various cancers [1,2,75]. Although the roles of PAF, PAFR and PAF-like lipids in cancer have been previously reviewed by Tsoupras *et al*. [2,32], Lordan *et al*. [1] and Melnikova and Bar-Eli [75], still some aspects on their multifaceted roles in tumor metastatic procedures and apoptotic procedures need to be further studied and re-evaluated.

Since PAF can activate several cells even at subpicomolar concentrations, through its binding on PAFR, PAF-levels in blood, cells, and tissues are tightly regulated by specific homeostatic metabolic pathways for its synthesis and catabolism. When the initial insult and its manifestations have been addressed by such an inflammatory response, then inflammation needs to be resolved by specific signaling that usually involves the activities of resolvins and the reduction of PAF-levels by the induction of PAF-catabolism [32]. More specifically, PAF is inactivated and catabolised by the removal of the acetyl-group on the sn-2 position of the phospholipid molecules by PAF-specific acetylhydrolase (PAF-AH, EC 3.1.1.47) to form its inactive for inflammation lyso-PAF form. The lyso-PAF is then reconverted into PAF or other phospholipids by the introduction of an acetyl group or an acyl group to the sn-2 position; hence, the biological cycle of PAF is spontaneously regulated [32,76].

Specific metabolic pathways for PAF-biosynthesis also exist that involve the activities of important enzymes, the regulation of which play crucial role in the continuation or not of PAF-synthesis and thus the maintenance or not of the PAF-related inflammatory stimuli. PAF is synthesised by many cells, usually as a response to specific stimuli, including but not limited to cytokines, endotoxins, and Ca^{2+} ionophores, through two distinctive enzymatic processes; the *de novo* and the remodelling pathways of PAF synthesis. Interestingly, PAF itself can induce both pathways [2,32], since binding of PAF on its receptor induce intracellular signaling [2,32,75], an occasion that results in an increase of its synthesis among other stimuli, while an increase of PAF levels by the induced cells or by paracrine cells or even by other types of cells, including tumor cells can further instigate PAF-synthesis by both pathways. More specifically, in the remodelling pathway, the not inflammatory active lyso-PAF is acetylated to PAF by isoforms of acetyl-CoA and lyso-PAF acetyltransferases (Lyso-PAF ATs, EC 2.3.1.67), notably *LPCAT1* and *LPCAT2* [76]. Lyso-PAF, the substrate for this enzymatic synthesis of PAF, is produced by the activities of the secreted or plasma form of PAF-AH, also known as lipoprotein-associated phospholipase A2 (Lp-PLA2) firstly Phospholipase A2 (PLA2), which catalyse the de-acylation/acetylation of the *sn2* acyl/acetyl groups of ethyl analogues of phosphatidylcholines present in cell membranes and/or in lipoproteins, including PAF and PAF-like molecules [32,76]. PAF production by *LPCAT2* is activated usually under acute inflammatory responses, but also during chronic inflammatory conditions [32,62], whereas the role of *LPCAT1* is still under investigation, but since it is calcium—independent, it seems that it does not participate in the inflammatory processes [76]. In the *de novo* pathway the main regulatory enzyme is a specific dithiolthreitol—insensitive cytidine diphosphate (CDP)-choline: 1-alkyl-2-acetyl-sn-glycerol cholinephosphotransferase (PAF-CPT, EC 2.7.8.2) that catalyses PAF production by the convertion of its substrate, 1-O-alkyl-2-acetyl-glycerol, to PAF [2,77].

PAF-CPT and lyso-PAF-AT both catalyse the final steps in each biosynthetic pathway and exhibit a basic regulatory role in PAF-production [32,76]. It has previously been proposed that the *de novo* pathway is responsible for endogenous PAF production and maintains normal physiological levels of PAF, whereas the remodelling route is implicated in a faster production of PAF, when the increase of its levels is acutely needed, including an acute response to an inflammatory stimuli. Nevertheless, it is now apparent that a long-term induction of PAF-CPT by the continuous presence of a risk factor, including the manifestations taking place within a tumor microenvironment, gradually increases systemic PAF levels with related consequences [2]. Furthermore, PAF-CPT activity seems to contribute to systemic inflammation and age-related malfunctions of the central nervous system and cancer [2,32,77], while its inhibition has provided beneficial outcomes in several chronic disorders [1,2,32,76,77]. Thus, the downregulation of both PAF-biosynthetic pathways and an upregulation of PAF-catabolism by specific anti-PAF bioactives seem to be an important approach to tackling PAF-induced thrombo-inflammatory manifestations [1,2,31,32,76].

However, it should also be noted that during several oxidative stress related thrombo-inflammatory manifesta-

tions, several reactive oxygen species also contribute to a non-enzymatic production of PAF and PAF-like molecules by instigating the oxidation of polar lipids (phospho-/glycol-lipids), either in cell membranes and/or in plasma lipoproteins, including low density lipoproteins (LDL) and high density lipoproteins (HDL). Thus produced PAF and its PAF-like oxidized phospholipids, can also further instigate an inflammatory stimuli by binding on PAFR, which also involves further induction of inflammation and its associated oxidative stress and thus increased PAF-levels, by both the enzymatic and the non-enzymatic PAF-synthesis. Subsequently, apart from the important beneficial roles of several anti-PAF bioactives against PAF-synthesis and activities, it is also highly important that the PAF-AH enzymes are also induced, since PAF-AHs have the capacity to indirectly terminate PAF-induced signalling pathways by directly reducing either enzymatic or oxidative upregulated increases of PAF levels [32]. On the other hand the plasma form of PAF-AH (LpPLA2) has also been proposed as a biomarker of inflammatory manifestations, probably due to its continuously increased levels and activities by the long-term presence of increased PAF-levels in such conditions, while recombinant PAF-AHs have also been proposed for anti-PAF benefits. Nevertheless more research is needed to fully elucidate the importance of PAF-metabolic enzymes and their regulation on PAF's involvement in cancer.

2.2.2 PAF-Pathophysiology in Cancer and Tumor Metastasis

Within the tumor microenvironment, PAF is independently or simultaneously produced by activated ECs, inflammatory cells (leukocytes, platelets etc.), and "cancer-stroked" cells [2,15,29]. The increased levels of produced PAF there, can then boost cancer progression and metastatic angiogenesis [1,3,28,72,73].

Tumor-originated factors inhibit leucocytes production (monocytes, macrophages, DCs etc.), otherwise the myelopoiesis procedure, within the tumor host, while they amplify the expansion of immature myeloid cells [75,78]. Multiple angiogenic tumor-derived agents/substances including cytokines such as Interleukins (IL) (mainly IL-6 and IL-10), VEGF, tumor necrosis factor alpha (TNF-α), etc., growth factors like TGF-β, Fibroblast Growth Factors α and β (FGF-α and FGF-β), Epidermal GF (EGF), etc. and their specific receptors, as well as prostaglandins and gangliosides, are implicated in myelopoiesis inhibition and cancer proliferation [2,75,78]. In addition, mean platelet volume relating to platelet activation and possibly the production of PAF and other inflammatory and growth factors has been also related to several cancers [79]. However, previous research to target specifically one factor and/or its' receptor at a time, has been halted due to tumors' continuous angiogenesis induction, where cancer cells adjust and reprogram other factors' production [2,80].

Interestingly, such tumor induced agents, cytokines and growth factors are also responsible for the induction and secretion of crucial lipid inflammatory mediators, including the induction of PAF-synthesis and expression of PAFR from the pre-mentioned activated endothelium within the tumor microenvironment and vice versa, while tumor cells themselves can also secrete PAF and express its receptor [2,45,46,81,82].

Several proinflammatory cytokines (TNF-α [36,83], IL-1β, IL-6, IL-8 and IL-12 [84,85]), chemokines (i.e., chemokines ligand-2 (CCL2) [86]), inflammatory enzymes like Cyclooxygenase-2 (COX2) and their eicosanoids products (arachidonic acid metabolites counting prostaglandins and leukotrienes), as well as vasoactive amines, bradykinin and growth factors involved in inflammatory signaling like the Vascular Endothelial Growth Factor (VEGF) [87], may along with the CXC-motif chemokine ligand 8 (CXCL8) [88] and MMPs that control the replacement of the ECM, be involved in PAF-signaling pathways [2,66]. Such interactions further induce an upregulation of angiogenesis in the tumor micro-environment, promoting carcinogenesis and metastasis [2,89,90] (Fig. 1).

Apart from CCL2, other inflammation-associated chemokines (C-X-C motif) and chemokines ligands (CXCL), such as CXCL1, CXCL2, CXCL3, CXCL5, CXCL6 and CXCL8, along with their respective chemokine receptors (CXCR), CC chemokine receptors (CCR), CX3C motif chemokine receptor (CX3CR), and "C" sub-family of chemokine receptor (XCR), with atypical chemokine receptors (ACKRs), are also implicated in these processes [91]. MMPs regulation reportedly holds an interesting potential role too, not only in anti-inflammatory action but also in anti-metastatic effects, especially when natural bioactives like the ginsenosides are used as therapeutic agents [92]. Considering they mediate the activation of ECM along with hemopoietic cells, their potential role in supporting malignancy through dysregulation of proper angiogenesis like MMP-9, does attract attention as an adjuvant or potential biomarker of anti-cancer therapies [93].

Cells that are affected by factors of paracrine pathways, create intracellular signal transduction pathways that influence the expression of other factors in the equilibrium of programmed cell death. The transcription factor NF-κB is normally part of the acute phase response, but when chronically activated it is linked to inhibiting the apoptosis of cancerous cells [39]. In other words, NF-κB, facilitates tumor growth mainly through nurturing and protecting malignant cells via autophagy regulation. However, autophagy in carcinogenesis can be characterized as a stimulus-dependent process [94]. This means that through NF-κB, tumor suppression and therefore a desirable anti-cancer effect can be acquired, as well. In essence, inhibiting NF-κB as a therapeutic target is still relevant [95,96], but understanding the dual role of NF-κB activation in can-

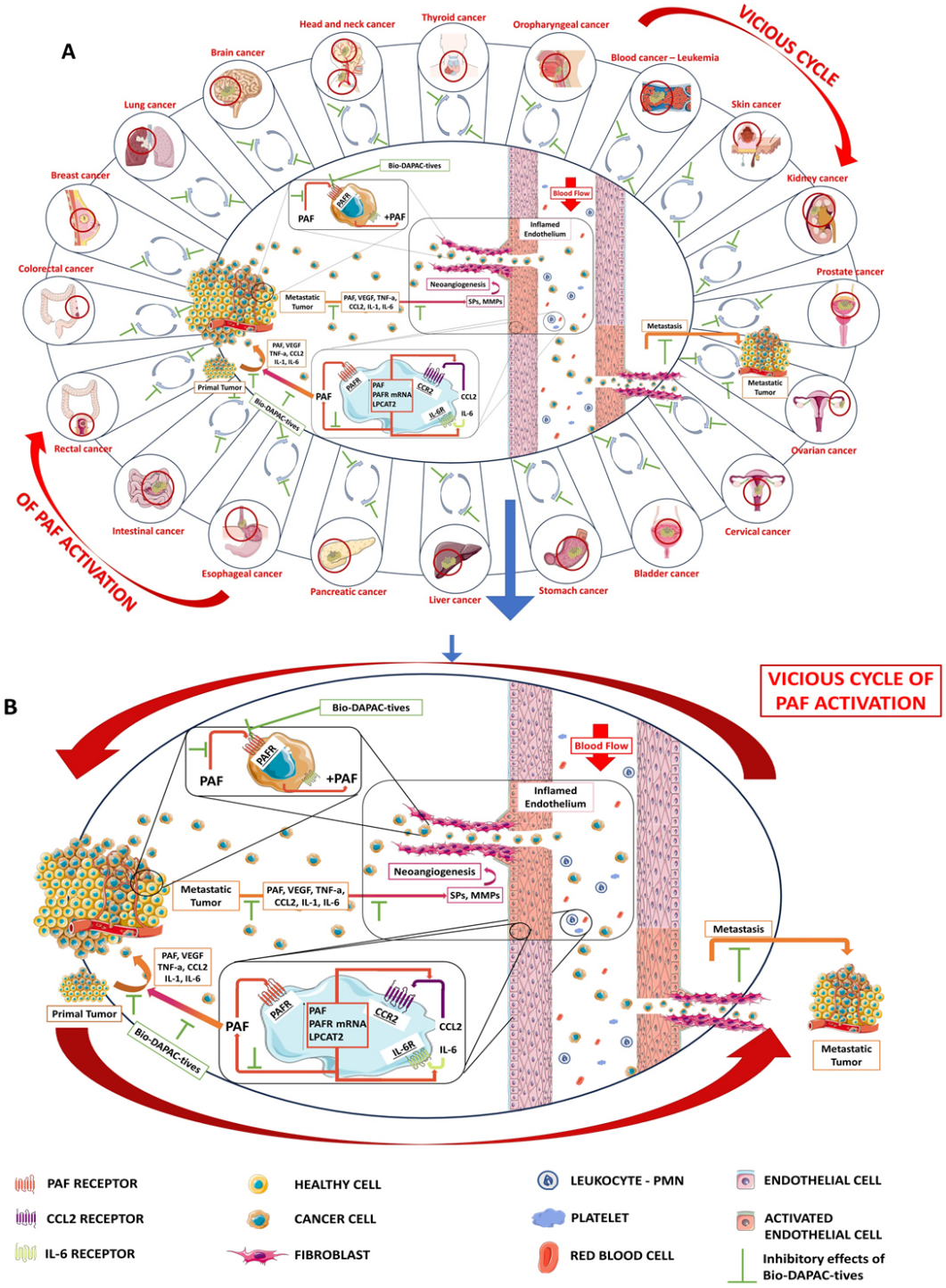


Fig. 2. The implication of PAF in tumor development and metastasis Potential benefits of Bio-DAPAC-tives. (A) Several types of tumors in which PAF and its vicious inflammatory and carcinogenic cycle are involved for their progression and metastasis. (B) Magnifying the involvement of PAF and its inflammatory pathways in tumor development, progression and metastasis and the beneficial inhibitory effects of Bio-DAPAC-tives against both PAF and PAF-associated vicious carginogenic cycle; inflamed blood cells and endothelium and/or primary tumor cells secrete PAF and other inflammatory cytokines and growth factors, which further propagate an inflammatory and carcinogenic PAF-related vicious cycle of a continuous synthesis of PAF and expression of PAF-receptor (PAFR), cytokines, growth factors and their associated receptors, with a subsequent signaling that favors and induce tumorigenesis and activation of both tumor cells and the endothelium towards tumor-induced neoangiogenesis and metastasis. PAF, platelet-activating factor; Bio-DAPAC-tives, Bioactives with dual Anti-PAF and Anti-Cancer activities; SPs, serine; LPCAT2, lysophosphatidylcholine acyltransferase 2.

cer is paramount for a further exploration of its ability to induce malignant cell apoptosis—simultaneously mirroring and facilitating the dual role of PAF/PAFR in the process [1,2].

Such an inflammation-related cascade involving all the aforementioned pathways, cells, mediators, genes and substances, finally leads to Cancer-Related Inflammation (CRI). CRI serves as a focus for pharmacological approaches aiming to alter the host microenvironment [36,69,70]. Concretely, pro-inflammatory mediators, like cytokines, chemokines and especially PAF and their receptors, are potent targets for upcoming biological remedies and therapies. In fact, CRI may provide an additional viewpoint to effective responses against tumor [36,69]. Several studies have reported that PAF and PAFR are interrelated with overall cancer development and the intrusion of several types of cancer [2], like the Epithelial Ovarian Cancer (EOC) [97].

Grasping the mechanisms of PAF activity, not only supports our better understanding towards cancer progression and the versatile impact of inflammation, but also may introduce potential new patterns in cancer treatment [2,32,76]. For example, breast cancer cells are able to express PAFR, and produce PAF *in-vitro*, when stimulated by cytokines like VEGF or TNF-α, concluding that metastatic cells are more receptive to PAF [75,98]. PAFs' discharge by the endothelium in the formulated tumor microenvironment is responsible for many sequential biological reactions, as not only it affects the neighboring—to the disrupted endothelium—endothelial cells, but also inflammatory and cancer cells to produce PAF and express PAFR [2,29].

Apart from its involvement in cancer, PAF is a phospholipid inflammatory mediator implicated in several thrombo-inflammatory processes and inflammation-related disorders [32], such as cardiovascular diseases (CVD) [32], neurodegenerative [99] and renal disorders [100], diabetes [101], allergy [102] and autoimmune disorders [103], as well as several persistent infections, including COVID-19 [104,105], HIV-induced infection [62], periodontitis [106], sepsis [107], leishmaniosis [108], etc. The binding of PAF on its 7-transmembrane G-protein-coupled PAFR initiates many intracellular signaling cascades, and then leads to various biochemical and functional pathways involved in the commencement and development of different cancers [1,2,29,74,76]. Moreover, the binding of PAF-like compounds to PAFR can also lead to various types of cellular activation in the PAF-signaling cascade, depending on the type of interaction (agonistic and/or antagonistic and/or inhibitory) [2,76,109–111].

The continuous presence of several risk factors associated with increased risk for several inflammation-related chronic disorders, including cancer and inflammatory metastatic manifestations, usually result in an induction and upregulation of PAF-synthesis, due to increased enzyme activities of both main regulatory enzymes of PAF-bisynthesis, PAF-CPT and Lyso-PAF-AT, as well as by oxidative stress induced non-enzymatic formation of PAF and PAF-like molecules, observed in such pathological situations. All the above usually conclude in upregulation of several inflammatory cascades, including that of the PAF/PAFR one, and a continuous inflammatory vicious cycle [32]. Such unfavorable PAF-induced inflammatory manifestations can in turn increase platelet and leukocyte reactivity and usually initiate endothelial dysfunction, which is a common step in several chronic disorders in which PAF and the PAF/PAFR signaling are implicated [32]. PAF-related inflammatory manifestations also take place inside the constructed tumor microenvironment and during inflammation-related tumor-induced angiogenesis, which usually result in tumor progression and metastasis [1,2,32].

PAF is plainly implicated in several cancer types such as digestive cancers, where patients suffering from gastric adenocarcinoma develop features like smaller-sized tumors, due to high PAFR expression [1,112,113]. The overproduction of PAF and over-expression of PAFR enhance tumor malignancy and cell proliferation as reported for example in hepatocellular carcinoma [114], in contrast to non-carcinoma specimens. Moreover, PAF is a crucial mediator in enhancing tumor neo-angiogenesis, with an ability to directly activate endothelial cells and indirectly mediate the process of angiogenesis. PAF's role in cancer metastasis is crucial, since its release by the activated endothelium induces cellular proliferation, the production of cytokines, growth factors or/and prostaglandins, and the expression of proteases (i.e., MMPs and SPs), all leading to signaling cascades and the inevitable ECM degradation involved in angiogenesis [2,36,115]. PAF has lately been identified as the inflammatory mediator involved in inciting and initiating the expression of all aforementioned angiogenic cytokine or growth factors, via the transcription factor NF-κB, thus it may provoke angiogenesis and tumor growth and metastasis [2,95,96,116]. PAF may also induce metastasis of non-tumorigenic cells, such as pancreatic, colon, lung, prostate, skin cells [110] and human brain meningioma due to its permeability of the blood brain barrier [1,117,118] (Fig. 2).

Cancer malignancy in PAF-related metastatic manifestations is also linked to the fact that cancer cells produce PAF themselves and express PAFR upon their membrane. For example, EGFR—evoked signaling increases PAF production in cervical and ovarian cancer cells, but the essential intertwinement between EGFR and PAF/PAFR axis, has yet to be explored [55,119–122]. Within the tumor microenvironment, PAF binding on its receptor can create interaction of tumor cells and endothelial cells that enhance cancer cell proliferation and a plethora of several intracellular signal transmissions, an intracellular state generated by the autonomous triggering of PAF mass production by cancer cells [2,29,73,116,123,124].

In many PAF-related reports, PAF's creation and binding to PAFR on the membrane surface of the above cells induce further PAF production, and thus the augmentation of angiogenesis. The exact timeline of the initial introduction of PAF inside the tumor microenvironment has yet to be fully clarified. Nevertheless, even in low intra-tumor PAF levels, PAF ensures proliferation, motility, neoplastic vessels' creation and ECM degeneration. In addition, PAF boosts cancer progression, cancerous cells' migration and adhesion molecules' expression and thus, metastatic angiogenesis and tumor certain development [2,3,29,73,74] (Fig. 2).

Despite the fact that cancer is highly associated with PAF activity, there is still limited evidence that all types of cancer are affected by its role, such as thyroid cancer [125]. At the same time, the PAF/PAFR axis functions also as an immune-suppressor by easily enhancing resilient dendritic cells (DCs) myeloid-suppressor cells' proliferation and as an advocate of modifications in the tumor microenvironment via the activation of MMPs and the triggering of VEGF production, through the NF-κB activation [29,30].

Latest insights have shown that PAFR and PAF-like molecules expression is induced by radiation and that the inhibition of PAFR augments the sensitivity of cervical and squamous carcinoma cells to treatment via radiation [126]. Thus, PAF, PAF-like molecules and PAFRs' signaling, may both directly and indirectly affect cancer and tumor progression [29]. Some carcinogenic outcomes deriving from PAF activity and pathways are displayed in Table 1 (Ref. [55,120,127–134]). Despite the fact that PAF is not the exclusive inflammatory mediator involved in cancer and tumor metastasis, it is one of the most crucial inflammatory and cancer-related mediators, the signaling and regulation of which must be fully elucidated.

Based on the above, several PAF-inhibitors of synthetic or natural origin, have been studied for reducing the PAF-related inflammatory burden during several chronic disorders [32], including cancer. These molecules can either inhibit the PAF/PAFR signaling and/or modulate PAF-metabolism. Promising results show bioactive compounds that display dual anti-PAF and anti-cancer activities (Bio-DAPAC-tives), which affect several stages of the involvement of PAF on tumor progression and development (Fig. 2). Concordantly, research regarding the implication of PAF and its signaling cascade, through NF-κB, in cancer development and progression, outlines its multifaceted role. Subsequently, the involvement of PAF in such tumor/inflammation induced manifestations needs further understanding, while the several anti-cancer approaches based on PAF-inhibitors also need to be further evaluated.

2.3 PAF's Dual Action—Ineffectual and Beneficial Effects in Cancer

By re-evaluating the existing progress in cancer research and the mediators involved, it can now be suggested that PAF's role in cancer is not so clear, rather than it is multifaceted. PAF may enhance tumorigenesis and metastasis but it may also serve as a beneficial mediator. For example, the increased expression of the PAFR has been proposed to be responsible for cell apoptosis via the activation of the transcription factor of NF-κB. In this context, the dual action—both beneficial and predisposing—of the NF-κB pathway also results in a dual action of the PAF/PAFR circuit [1]. In Tables 1,2, both PAF/PAFR associated carcinogenic and anti-carcinogenic outcomes are presented, respectively. It should be stressed out that favorable involvement of PAF, PAFR and their associated signaling in anti-cancer approaches are mainly focused on PAF's crucial involvement in conventional anti-cancer strategies and treatment, mainly through the PAFR antagonists' potential and the activities of dietary or medicinal PAF-inhibitors.

Interestingly, PAF can also facilitate apoptotic cancer cell death (Table 2, Ref. [55,120,126,127,130,132,134–137]) while it stimulates eryptosis [138,139]. It is noted that the programmed cell death spectrum includes oncosis, eryptosis/erythrocyte apoptosis, apoptosis, pyroptosis, and necrosis [140]. Anti-tumor effect through cell cycle intervention measures is quite common, showing PAF/PAFR involvement in some cases (Table 2). PAF-related eryptosis, highlights its dual role in cancer. Eryptosis protects from intravascular hemolysis, but inflammation and cancer can cause upregulation of signaling pathways that favor it. Moreover, eryptosis is a basis of cancer-evoked anemia which worsens with certain cytotoxic treatments [141]. PAF can cause this suicidal death of erythrocytes and PAF antagonists can logically prevent it, a mechanism that could support enhanced anti-cancer cytostatic therapies, since such drugs can induce eryptosis of non-malignant cells as well [142].

Nevertheless, PAF and cell death interactions are not limited to cancer-specific eryptosis. PAF and PAFR are involved in the inhibition of neuronal pyroptosis, demonstrating neuroprotective results after after ischemia/reperfusion (I/R) injury [143]. Depending on the cancer type and progression stage, anti-PAF approaches can encompass both positive and negative effects, a characteristic that increases current research interests concerning dual anti-PAF and anti-cancer drug development.

2.4 Interaction(s) of PAF with Anti-Cancer Drug-Based Strategies

The implication of PAF in cancer formation, development and growth, as well as tumors' abilities to go unnoticed and eventually even recruit immunologic and inflammatory agents to survive anti-cancer strategies has also shed light on the importance of the interaction of PAF and its' signaling with all types of anti-cancer approaches. PAF's therapeutic and promoting role in cancer progression includes the fluctuation of PAF-like molecules concentrations along with PAFR's transcription degree and the intera-

Table 1. The implication of PAF, its receptor, metabolism and signaling pathways in carcinogenic and metastatic procedures.

Inflammatory Pathways	Model	Study Design	Outcomes	Main Outcomes - Conclusions	References
LCAT2-PAF PAFR Ras-Raf-MEK-ERK PI3K-Akt-mTOR	● Cervical Cancer Samples: CASKI and C33A cells.	● Evaluation of the relation between the upregulations of LPCAT2 and cPLA2, and prognosis in cervical cancer in the cBioPortal platform. ● Treatment of CASKI and C33A cells with cetuximab and EGF each, for gene expression assays of PAFR and LPCAT2 and for a cell migration assay, after starving. ● Treatment of CASKI cells with PD98059 (MEK inhibitor). ● Treatment of CASKI cells with LY294002 (PI3K inhibitor).	● The upregulation of LPCAT2 and cPLA2 shows a negative prognosis for cervical cancer patients. ● The highest concentration of EGF increased the expression of both PAF elements. Pre-incubation with cetuximab blocks EGF's effects. ● PAF supports an increase in the motility of this cell line. EGFR inhibition with cetuximab reverses such a phenomenon. ● Inhibition successfully reversed EGF-mediated PAFR and LPCAT2 induction. ● Inhibition did not completely reverse EGF-mediated PAFR and LPCAT2 induction.	● EGFR expression and activation positively correlated with mRNA expression of elements of the PAF pathway in CC Samples, via ERK/MAPK pathway. Specifically, LPCAT2 upregulation is connected to unfavorable clinical outcomes in CC patients with PAF inducing the transactivation of both EGFR and other downstream signaling pathways.	[55]
PAFR-evoked signaling pathways	● Ovarian Cancer cell line SKOV3 and A2780.	● Treatment of cells with PAF, WEB2086 and with PAF + WEB2086 together to examine their effect on stemness-related gene expression and CSC markers.	● PAF promoted the spheroid-formation ability of SKOV3 and A2780 cells increasing spheres' numbers and sizes. ● The upregulation of the expression of several stemness genes (*Oct4*, *nanog*, *klf4*, *c-myc*, *lgr5*, *CD24*, *CD34*, and *ALDH1*) and CD44+CD133 cells (SKOV3) and CD133 (A2780) was observed.	● The specific PAFR inhibitors WEB2086 and GB may constitute a promising treatment strategy for non-mucinous ovarian cancer.	[127]
PAFR-evoked signaling pathways	● (HUC), (HTB-9) and (HT-1376) cells. ● (HBMEC), (HTB-9) and (HT-1376) cells.	● Incubation with CSE and with or without (S)-BEL (iPLA2β Inhibitor). ● Incubation of (HBMEC). Incubation of (HTB-9) and (HT-1376) cells with CSE and pretreatment with (S-BEL) and Ginkgolide B (PAFR antagonist).	● CSE incubation results in significant PAFR expression and PAF production which can be blocked by pretreatment with (S)-BEL in all cells. ● CSE incubation increases adherence of bladder cancer cells to bladder endothelial cells, diminishable with pretreatment of (S-BEL) and Ginkgolide B.	● Blocking PAF accumulation or the PAFR could be used as a potential therapeutic target to inhibit bladder tumor cell transmigration across the bladder endothelium.	[128]
PI3K/AKT	● MCF10A cell line.	● Treatment of 3D cultures with and without PAF and immunostaining with Ki67, polarity and cell-cell junction marker, immunoblotting with EMT markers separately. ● Soft agar assay on dissociated cells of both control and PAF-treated acini stained with MTT.	● 80% of the PAF-treated acini were found to be hyperproliferating with (FWHM) values significantly higher in PAF-exposed cells when compared to untreated dissociated cells and PAF-induced partial (EMT)-like phenotype were observed. ● PAF dissociated cells could form colonies in an anchorage-independent manner.	● PAF induces a transformation phenotype on the MCF10A cell line altering epithelial polarity causing loss and/or disruption of cell-cell junctions. PAF-induced EMT-like Phenotype can be connected with poor survival and therapy resistance in the same cell line since PAF can induce *in-vitro* tumorigenesis.	[129]
Wnt/β-catenin	● HCC1937 (BRCA1 negative cell line).	● Downregulation of *PLA2G7*/PAF-AH by siRNA knockdown.	● Increased viability and proliferation rate of HCC1937 cells were observed.	● *PLA2G7* silencing favors cancer progression by an increase in viability, proliferation, and migration of BC cells.	[130]
STAT3	● HCC tissues. ● Four hepatoma cell lines HepG2, Hep3B, Huh7 and Hcclm3.	● Kaplan-Meier survival analysis on mRNA expression patterns of PAFR in HCC tissues obtained from GEO and TCGA-LIHC/GTEx datasets. ● Treatment of HCC cells with different concentrations of PAF for cell viability and cell migration assay.	● Liver cancer patients with high PAFR expression had a marginally worse prognosis with lower survival time, than those patients with low PAFR expression. ● HCC cells exhibited a higher migratory potential with the treatment of 50 nm PAF.	● PAF plays a negative role in HCC prognosis possibly via supporting metastasis.	[131]

Table 1. Continued.

Inflammatory Pathways	Model	Study Design	Outcomes	Main Outcomes - Conclusions	References
Apoptotic signaling and VEGFA-VEGFR2 signaling pathways-(suspected)	● (HOSE cells).	● Transient over-expression studies on normal HOSE and transfected with PAF-AH 1B2 WT or blank vector cells were conducted.	● Overexpression of PAF-AH IB2 caused Caspase-8 activation and normal ovarian epithelium died.	● PAF-AH IB2 as potential marker of normal ovarian epithelium health.	[132]
PAF/PAFR pathway	● Ovarian serous carcinoma cell lines: SKOV3, DOV13, OVCA433. ● Clear cell carcinoma cell lines: ES2 and TOV112D. ● Mucinous OCC lines: RMUG-L, 3AO, OMC685.	● Treatment with MSC-CM. ● Grown in MSC-CM and treatment with different PAF concentrations (positive control) and GB (negative control). ● Treatment with MSC-CM, PAF (100 nmol/L) and GB (100 µmol/L) on SKOV3 cells. ● Treatment of SKOV3 cells with PAF (100 nmol/L) alone or with GB (10 µmol/L). Cultured in MSC-CM and stained for immunofluorescence analysis.	● MSC-CM promotes the proliferation of (PAFR+): SKOV3, DOV13, OVCA433, ES2 and TOV112D but does not in (PAFR-) cell lines: MUG-L, 3AO, OMC685. ● SKOV3 cells showed increased dose-dependent proliferation after 24 h of treatment with PAF (10 nmol/L), (100 nmol/L) and MSC-CM. ● The MSC-CM-induced proliferation increase was comparable to that of PAF (100 nmol/L), in SKOV3 migration ability was similar as well ● Co-treatment of the positive control with GB (100 µmol/L) showed complete inhibition of PAF-evoked proliferation and cell migration while OMC685 showed no differentiation. ● The expression of cyclin D1 and the site-specific phosphorylation of FAK, simultaneously increased in cells cultured in MSC-CM and treated with PAF (100 nmol/L) compared with that in control cells. ● GB addition reduced the staining intensity of both proteins.	● Ovarian serous carcinoma cell lines: SKOV3, DOV13, OVCA433. ● Clear cell carcinoma cell lines: ES2 and TOV112D. ● Mucinous OCC lines: RMUG-L, 3AO, OMC685.	[133]
PAF/PAFR pathway	● SKOV3-derived subcutaneous tumors in BALB/c nude mice.	● Mice were subcutaneously injected with SKOV3 cells alone or with MSCs/RFP at different ratios. Mice in the WEB2086 group were injected with WEB2086 and mice in the control group, were injected with DMSO.	● MSCs alone were not tumorigenic but the growth of SKOV3-derived subcutaneous tumors was promoted. WEB2086 blocked this effect. Compared with the SKOV3 + WEB2086 group, the SKOV3 + MSC + WEB2086 group exhibited a significantly larger tumor volume. ● High PAF concentration and PAFR expression in tumor tissue from mice injected with SKOV3. MSCs/RFP could be visualized in the tumor stroma in the co-injection groups. Mice in the WEB2086 group had higher weights than the mice in the DMSO group did.	● MSCs can promote the proliferation of OC through the PAF/PAFR pathway, but since the PAFR inhibitor could not completely inhibit the tumor-promoting effect of MSCs, other mechanisms may also be involved. ● When co-injected with SKOV3 cells, MSCs can settle at the injection site and participate in the formation of the tumor stroma. Potential crosstalk between MSCs and SKOV3 cells. ● The inhibitor ameliorated the systemic effects of PAF/PAFR signaling.	[133]

Table 1. Continued.

Inflammatory Pathways	Model	Study Design	Outcomes	Main Outcomes - Conclusions	References
PAFR/Stat3 axis	● Three paired ESCC cells and CAFs extracted from ESCC tissues.	● Identification of common targets between ESCC cells and CAFs through genome-wide analysis of transcriptional targets of pStat3 Tyr^{705}. ● Quantitative ChIP, real-time (PCR) and immunoblotting. ● Kaplan-Meier analysis. ● ESCC grown in CAFs derived CM. ● Planting ESCC on matrigel-coated inserts with CAFs in the lower wells in Boyden chambers. ● Co-culture and gene expression array on KYSE150 cells.	● PAFR was consistently found to be one of the most abundant Stat3-binding promoters. ● Inhibition of Stat3 by either stable knockdown of Stat3 or treatment with S3I201 (Stat3 inhibitor) effectively reduced PAFR expression at both transcriptional and posttranscriptional levels in ESCC (primary ESCC cells, ESCC cell lines: KYSE410 and KYSE150) and CAFs. ● PAFR or pStat3 Tyr^{705} expression in tumors positively correlated with pStat3 or PAFR expression in CAFs, respectively. ● ESCC cells grown in CAFs-derived CM displayed a larger growth ability than ESCC cells alone while ESCC cells grown with Stat3 or PAFR-depleted CAFs, derived CM, didn't have a growth increase compared to ESCC alone. ● PAFR or Stat3 depletion effectively inhibited the invasion of ESCC cells compared with control ESCC cells.	● Stat3 regulates PAFR expression both in tumor and CAFs with both stromal pStat3/tumor PAFR and tumor pStat3/stromal PAFR group being able to help predict patients' survival, effectively. ● Crosstalk of PAFR/Stat3 signaling between ESCC cells and CAFs promotes tumor malignancy *in-vitro*. The stromal PAFR/Stat3 axis can support malignancy, in tumor cells and through CAFs.	[134]
PAFR/Stat3 axis (*in-vivo*)	● Co-implantation of KYSE410 or KYSE150 cells into mice subcutaneously, with PAFR/Stat3-positive control or PAFR/Stat3-knockdown CAFs	● Tumor volume and proliferation index analysis.	● CAFs effectively induced tumor growth of ESCC compared with ESCC tumor alone. ● PAFR-depleted ESCC tumors grew slower than control ESCC tumors. ● Stat3-depleted ESCC tumors grew slower than control ESCC tumors even when co-injected with CAFs.	● PAFR/Stat3 crosstalk between tumors and CAFs plays a role in the malignant progression of tumors *in-vivo*.	[134]
PAF/PAFR pathway	● OC samples from EOC surgery recipients (BRCA status unknown)	● Correlation between cytoplasmic PAFR expression and clinicopathological data.	● Patients with higher PAFR expression were fewer compared to those with lower expression.	● PAFR as a negative prognostic factor in OC patients.	[120]

Abbreviations: CSE, Cigarette smoke Extract; HUC, Primary Human Urothelial Cells; HTB-9, Human grade II Urinary Bladder carcinoma cells; HT-1376, Human grade III Urinary Bladder carcinoma cells; HBMEC, Human Bladder Microvascular Endothelial Cells; FWHM, Full Width Half Max; EMT, Epithelial-Mesenchymal Transition-like phenotype; HOSE cells, Normal Human Ovarian Surface Epithelial cells; OC, Ovarian cancer; EOC, Epithelial Ovarian Cancer; CAFs, cancer-associated fibroblasts; ESCC, Esophageal cancer; MSC-CM, Mesenchymal stem cell - derived conditioned medium; GB, Gallbladder; MSCs/RFP, mesenchymal stem cells/Red Fluorescent Protein; DMSO, Dimethyl sulfoxide; PLA2G7, lipoprotein-associated calcium-independent phospholipase A2 group VII; CSC, Cancer stem cell; CC, Cervical Cancer; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; GEO, Gene Expression Omnibus; TCGA, The Cancer Genome Atlas; LIHC, liver hepatocellular carcinoma; GTEx, Genotype-Tissue Expression Program; (S)-BEL, (S)-Bromoenol lactone; PI3K, Phosphoinositide 3-kinase; PAF-AH IB2, Platelet-activating factor acetyl hydrolase IB2; WT, wild type.

Table 2. Anti-Cancer outcomes of Anti-PAF interventions with Bio-DAPAC-tives.

Intracellular Inflammatory Pathways	Model	Study Design	Outcomes	Main Outcomes - Conclusions	Ref.
Wnt/β-catenin	● *BRCA1* mutant ovarian cancer cells.	● Analysis of PAF-AH, pGSK3b and b-catenin expression. ● PAF-AH expression was investigated in OC tissue and serum of *BRCA1* mutation carriers. ● *In-vitro* experiments were performed to assess cell viability, proliferation and moving capacity of *BRCA1* mutant OC cells after *PLA2G7* silencing.	● The association of PAF-AH with b-catenin and pGSK3β was strong.	● PAF-AH can be an independent positive prognostic factor for overall survival on *BRCA1* mutant OC. Downregulation of Wnt/b-catenin pathway could mediate its protective character. Use of PAF-AH as a biomarker for patients with *BRCA1*-negative OC should be explored.	[130]
MAPK Pathway (p38 and ERK1/2)	● PANC-1 cells (PAFR-expressing) and Hs766T cells (PAFR-deficient).	● Treatment of PANC-1 and Hs766T (for control) cells with WEB2086, followed by treatments with or without gemcitabine, PMA, or CPAF.	● WEB2086 significantly attenuated gemcitabine- and CPAF-mediated, but not PMA-induced, MVP release in PANC-1 cells.	● Gemcitabine induces MVP release in a PAFR-dependent manner, MVPs are linked to resistance and therefore, PAFR inhibitors can be used as an adjuvant to gemcitabine-treated PANC1 cells.	[135]
EGFR-evoked signaling pathways	● Cervical Cancer Sample - CASKI and C33A cells.	● Treatment CASKI cells with combined cetuximab and WEB2086 for a post-treatment viability study.	● The combination of WEB2086 + cetuximab compromised CASKI cells' viability by about 37% while isolated treatment, decreased cell viability by approximately 18% and 25%, respectively.	● Combined inhibition of PAFR and EGFR impairs the clonogenic capacity of aggressive CC cells, holding significant therapeutic potential.	[55]
PAF/PAFR	● Ovarian Cancer cell line SKOV3 and A2780.	● Treatment of SKOV3 and A2780 cells with PAF and then observing the cell distribution cycle compared to treatment with DMSO and WEB2086.	● PAF inhibited the transition of quiescent SKOV3 cells into the cell cycle, increasing the percentage of G0/G1-phase cells. The cell cycle delay was accompanied by a decreased percentage of S-phase cells.	● WEB2086 and GB may constitute a promising treatment strategy for non-mucinous OC.	[127]
PAF/PAFR	● Cervical cancer-derived cell lines (C33A, SiHa, and HeLa). ● Human carcinoma cell lines: KBM (PAFR–) and KBP (PAFR+).	● Treatment of the cells with and without CV3938 (PAFR antagonist) before irradiation (4 or 8 GY). ● Irradiation of all cell lines (4 or 8 GY). ● Treatment of the cells with and without CV3938 (PAFR antagonist) and Indomethacin (COX Inhibitor) before irradiation.	● PAFR antagonist enhances cell death induced by radiotherapy in all cases. ● The PAFR+ cells survived more than the PAFR− cells. ● CV3938 significantly increased radiation-induced cell death, whereas indomethacin did not affect cell survival.	● The combination of RT with a PAFR antagonist could be a promising strategy for cancer treatment.	[126]

Table 2. Continued.

Intracellular Inflammatory Pathways	Model	Study Design	Outcomes	Main Outcomes - Conclusions	Ref.
PAF/PAFR	● GEPIA Cancer Genomic database. ● MCAS and SKOV3.	● Data analysis. ● Ovarian tumor tissue microarray. ● Transduction of PAF-AH IB2 wild-type cell lines (Control) and PAF-AH IB2 knockdown cells with control shRNA or PAF-AH IB2 shRNA constructs.	● Patients of ovarian cancer with higher levels of PAF-AH 1B2 expression had a significantly shorter survival time. ● Compared to human normal ovarian epithelium (HOSE II, HOSE 2282) PAF-AH IB2 was over-expressed in MCAS, SKOV3, Tov112D, OVCA3, OVCA420, OVCA432, OVCA633, OVCA810 and RMUGL cell lines. ● The knockdown cell lines showed a significantly lower ability to form colonies *in-vitro* in soft agar, a significantly slower rate of proliferation and a decrease in cell migratory capacities.	● PAF-AH IB2 can be a potential therapy target since it can mediate malignant proliferation and migration in OC cells.	[132]
LPCAT1-4	● Melanoma cell lines: A375 and SK-MEL-5.	● Irradiation of *LPCATs1-4* silenced cells –RNA rings with siRNAs and simply with free siRNAs. ● Increased percentage of apoptotic cells in the *LPCATs1-4* silenced cells compared to non-silenced.	● Increase in subG1 percentage in non-irradiated cells and noticeable detachment along with cell number reduction when irradiated – in *LPCAT1-4* silencing. ● Bigger percentage of activated caspase 3/7 in the silenced group compared to the control.	● Silenced cells are more vulnerable to irradiation therapy since they show reduced survival time and bigger apoptosis percentage.	[136]
PAF/PAFR	● OVCAR-3, WB1.289, ES-2, and TOV 112D.	● Treatment of cells with different concentrations of Rupatadine (PAFR antagonist).	● Reduced proliferation and migration ability of OC cells.	● Rupatadine can inhibit the proliferation and migration of OC cell lines.	[120]
PAF/PAFR (PAF-like family)	● MCF-7 and MDA-MB-231.	● BrdU incorporation.	● Inositol-C2-PAF inhibits the growth, and migration of these cell lines.	● Inositol-C2-PAF can potentially be used as an adjuvant to BC therapy.	[137]
PAFR/Stat3 axis (*in-vivo*)	● ESCC tumor cells were co-injected with CAFs subcutaneously into the right flank of nude mice.	● Treatment of the tumor-bearing mice with S3I-201, etizolam, and both.	● Inhibition of PAFR/Stat3 axis between tumor and CAF. ● Cotreatment decreased tumor volume in comparison with both low and high doses of each agent alone.	● PAFR and Stat3 inhibitors synergize in suppressing tumor growth *in-vivo*.	[134]

Abbreviations: Bio-DAPAC-tives, Bioactives with dual anti-PAF and anti-cancer activities; BMMs, Bone Marrow Monocytes; Trap, Tartrate-Resistant Acid Phosphatase; RANKL, Receptor Activator for NF-κB Ligand; EOC, Epithelial Ovarian Cancer; BrdU, Bromodeoxyuridine; MCAS, Mast Cell Activation Syndrome; MVP, Major Vault Protein.

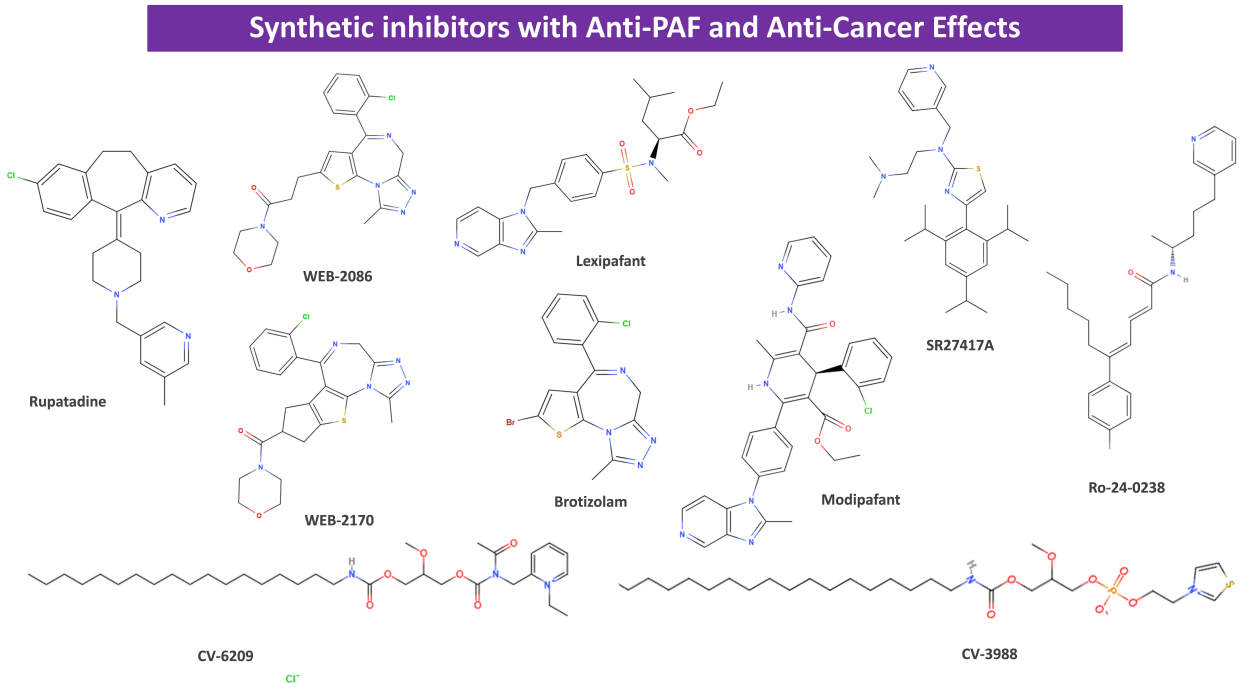


Fig. 3. Synthetic specific PAF-inhibitors with both anti-PAF and anti-cancer activities.

ction with anti-cancer chemo-therapeutics, regardless of adjuvants. Immunotherapy may be active or passive [144] and with the use of novel biological agents, more toxicity concerns may be present. Cytokine Release Syndrome (CRS) involves a potentially lethal response to such therapies against cancer, like adoptive T-cell usage [145]. PAF has not been confirmed to mediate the CRS progression. This aspect can be addressed in the future especially since PAF remodeling has already been characterized as a focus point for Chimera Antigen Receptor (CAR) T-cell therapy enhancement for patients with multiple myeloma [146].

PAF inhibitors and PAFR antagonists show favorable results either when solely used as an anti-PAF anti-tumor approach or when they are used in combination with cytotoxic anti-cancer treatments. Recent data has shed light to the mechanism with which anti-cancer drugs may upregulate PAF production creating a negative health effect, against their initial intended cause [147]. It is therefore clear that co-treatment with PAF-inhibitors and PAFR antagonists along with traditional anti-cancer drugs needs further study.

3. PAF-Related Mitigation Efforts against Cancer

Many endogenous or ingested PAF inhibitors have been suggested in the past few years as potential PAF-activity suppressors in a plethora of physiological and cancer therapeutic/disease prevention procedures [76,123,148]. Since PAF antagonists circulate in the human body, it was hypothesized that their absence could increase PAF activity [32,76]. Nevertheless, the discovery of PAF antagonists of synthetic and natural origin, including dietary PAF inhibitors, have been thoroughly assessed and evaluated for their potential inhibitory effect against the uncontrollable PAF cancer-inducing action [2,32,123,149]. PAF inhibitors are classified through several ways, including their natural or synthetic origin [76,123,150], their various chemical structures or their interaction with the PAF receptor [123].

According to their specificity, PAF inhibitors are categorized as non-specific and specific inhibitors [76,123]. Non-specific PAF inhibitors encompass compounds able to impede certain actions within PAF-triggered signal transduction pathways. G-protein inhibitors or calcium channel blockers are only a few of the many non-specific PAF inhibitors, that are of low importance since they lack specificity [123,151]. Specific PAF inhibitors that completely or incompletely bind to the PAFR, have a potential therapeutic value as shown by *in-vitro* studies and animal models [76,123,150]. For example, some PAFR specific antagonists with proved anti-cancer activity are the synthetic ginkgolides BN-50730, BN-50739 and BN-52021 [34,82,152], WEB-2086 and WEB-2170 [34,152], CV-3988 [152,153] etc., that are suggested as potent anti-cancer agents [2]. Moreover, considering the structure-activity relationships of PAF inhibitors, several dietary polar lipids [154], nitrogen heterocyclic compounds, phenolics and other compounds that affect the PAF/PAFR are promising [123,155]. Several studies on synthetic and natural PAF inhibitors as well as dietary PAF-antagonists, which reduce and/or inhibit cancer-related PAF activities are further outlined.

3.1 Synthetic Molecules with Anti-PAF and/or Anti-Cancer Effects

Since established evidence supported the anti-cancer effects of PAF inhibitors, many synthetic inhibitors possessing anti-PAF, anti-cancer or both actions have been introduced [123]. Specifically, the first PAF-like molecule that was discovered in 1983 and is reported as a synthetic PAFR antagonist is a thiazolium derivative namely CV-3988 [150,152,153]. More recent reports, have outlined that this specific PAF-inhibitor exhibits significant *in-vivo* and *in-vitro* anti-PAF activity [1,156] and anti-cancer properties, since it notably reduced the development of new vessels in a tumor generated by subcutaneously implanted MDA-MB231 breast cancer cell lines in SCID mice [34]. Additionally, benzodiazepines derivatives, including one thienodiazepine, commonly "brotizolam" [156], with anti-PAF effects against PAF-induced platelet aggregation [157,158], have also exhibited protective effects against cancer-induced anxiety and dyspnea [159]. Moreover, hetrazepine derivatives like the thienotriazolodiazepine WEB-2086 and WEB-2170 are selective PAFR antagonists [150,160,161], as well as potent inhibitors of cancer proliferation in human solid tumor cell lines, like MCF-7 and MDA-MB-231 breast adenocarcinoma cells [162]. WEB-2086 was successfully used against Ultraviolet B (UVB) radiation-induced dermatitis as well [163]. Moreover, WEB-2170 can dose-dependently inhibit *in-vitro* the PAF-induced platelet aggregation [164], while muscle infusion of this PAF-antagonist during reperfusion inhibited neutrophil infiltration [165]. In parallel, WEB-2170 showed anti-cancer effects in combination with dacarbazine (chemotherapeutic drug) in reducing tumor volume in mice and increasing the survival of animals with tumors in a murine melanoma model [1,166].

Some of the first synthesized molecules, shared a PAF-like glycerol backbone including the aforementioned CV-3988 [123], plus CV-6209 [167,168], ONO-6240 [169] and Ro 19-3704 [170], while later on, this glycerol backbone was replaced by a cyclic structure so as to form molecules like SRI-63441 [171] or UR-11353 [172] (Fig. 3). All the above molecules are depicted as potent—PAF-like—PAF and PAFR antagonists, mainly *in-vitro* [167,168,171,172] and *in-vivo* [168–170]. Of these synthetic PAF-inhibitors, CV-6209 displayed strong anti-tumoral effect when infused at low concentrations in *in-vitro* cultured human glioma cells [173] and *in-vivo* mainly in CT26 tumor-bearing mice [174]. Nevertheless, recently collected data showed that Ro 24-238 as well as other PAF-antagonists like Lexipafant, Modipafant and SR27417A [175], with promising anti-PAF protection against asthma [176], were unable to easily enter the affected tissues' cell interior so as to prevent PAFR's nuclear transcription, while SR27417A did not show safe evidence of its treatment effectiveness against acute ulcerative colitis or cancer [177].

Another important synthetic specific PAF-antagonist, Rupatadine, possesses a dual functional role: it is both an oral PAFR and an effective histamine H (1)-receptor antagonist [178,179]. This anti-PAF inhibitor, has been successfully utilized in order to treat allergic rhinitis [179,180]. Lately, when it was used in human Mast cells (MCs) line LAD2 and primary human lung tissue MCs (hLMCs) in cooperation with CV6209, it showed efficacy in inhibiting MC cancer degranulation at both types of cell lines [181]. Rupatadine synthetic inhibitor was also characterized as a prognostic ovarian cancer marker, since it notably inhibited—in a recent *in-vitro* clinical trial—cell migration and proliferation of ovarian cells [120]. All positive proved outcomes deriving from Rupatadine's use, led to the mass production of the first circulating drug, under the commercial name "Rupafin" [123], which is widely preferred in the systemic treatment of allergic disorders [182].

In the last decade, another class of synthetic molecules with potential anti-PAF and anti-cancer benefits has been reported. Several "metal-based inflammatory mediators" with potent anti-platelet properties against several pathways of platelet activation and aggregation have strong anti-PAF and anti-thrombin effects at very low concentrations [35]. Since both PAF and thrombin are implicated in cancer formation and metastasis [2], Philippopoulos and co-workers [123] reported a series of chromium(III), manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II) complexes with strong anti-PAF and anti-thrombin properties that can also be utilized against several cancers. Based on the reported preliminary Structure-Activity Relationship (SAR) data reported, a synergetic effect indicates the positive effect of ligand coordination to a metal center, that generally leads in an increase of the anti-PAF (antiplatelet activity) of the relevant compound [123]. Interestingly, it was determined that the activities of a series of metal complexes (expressed as IC_{50} values) against the PAF-induced platelet aggregation were comparable with the inhibitory effect of known natural PAF antagonists from the series of Gingolides B [183], along with that of rupatadine. Additionally, some of these complexes showed an activity against PAF-basic biosynthetic and catabolic enzymatic pathways in rabbit leukocytes, underlying their potent anti-inflammatory properties [35]. The 2-(2′-pyridyl)quinoxaline (pqx) ligand comprising these metal complexes with significant anti-PAF and anti-thrombin potencies was not solely active towards PAF and thrombin. In cellular proliferation studies from our group, pqx ligand precursor was found to be quite cytotoxic in tumor-derived HeLa cells, but its toxicity was reduced upon complexation to Cr(III), Co(II), Zn(II) Mn(II), Fe(II) and Ni(II) respectively. Interestingly, Cu-pqx was found to be more effective than cisplatin, as PAF-inhibitor expressed as IC_{50} values.

Moreover, a library of several metal-based complexes of Rh(I)/Rh(III) and Ru(II)/Ru(III) as potent specific in-

hibitors of PAF has been reported, with very strong anti-PAF effects at a nanomolar to micromolar scale [184–188]. For some of these metal-based complexes molecular docking calculations illustrated that they can be accommodated within the ligand-binding site of PAFR and thus block PAF activity with a specific antagonistic effect against PAF. These results, along with the observed anti-ADP and anti-thromin antiplatelet properties of these complexes (rhodium case), further suggest that they can be considered as metal-based PAF inhibitors with promising antiplatelet, antithrombotic, and anti-inflammatory activities. Nevertheless, some bulkier octahedral Rh(III) complexes that could not fit into the ligand binding domain of PAFR, could instead potentially exhibit their anti-PAF activity at the extracellular domain of PAFR.

Remarkably, two of these Ru-based PAF inhibitors (complexes 25 and 26 that are displayed in Fig. 3) exhibited comparable biological activity with rupatadine fumarate, a potent PAF receptor antagonist (0.26 μM), as previously stated [178]. *In-vitro* cellular proliferation studies of these two Ru-based PAF inhibitors against a range of cell lines (HEK-293 and breast cancer cell lines MCF-7 and MDA-MB-468) showed that the one with nanomolar potent anti-PAF effect (IC_{50} = 0.18 μM against PAF) was less cytotoxic (60.2% viability on HEK-293 cells) compared to the well-established cisplatin (10.3% viability), that has an IC_{50} value of 0.55 μM against PAF (Fig. 4). Additionally, for the same Ru-based metal complex a moderate activity (66.5% and 70% viability) was found on MCF-7 and MDA-MB-468 cancer cells. On the other hand, the second Ru-based complex proved less potent against MCF-7 (81% viability) and MDA-MB-468 (85% viability) cancer cell lines, which further illustrates the importance of structure activity relationships for these metal complexes.

In line with the results reported above for the ruthenium inhibitors, strong anti-PAF effect in platelets have been recorded with some organometallic tin(II) and tin(IV) complexes bearing bulky oxygen tripodal ligands. Molecular docking calculations illustrated that these organotin analogues cannot fit inside the PAF-binding site PAFR, suggesting that they can interact with the extracellular domain of the receptor, probably inhibiting PAFR by blocking the entrance of PAF inside its receptor [180]. Interestingly, two of these organotin complexes were also evaluated for anti-tumor activity, on human Jurkat T lymphoblastic tumor cell line and found to be more effective than cisplatin.

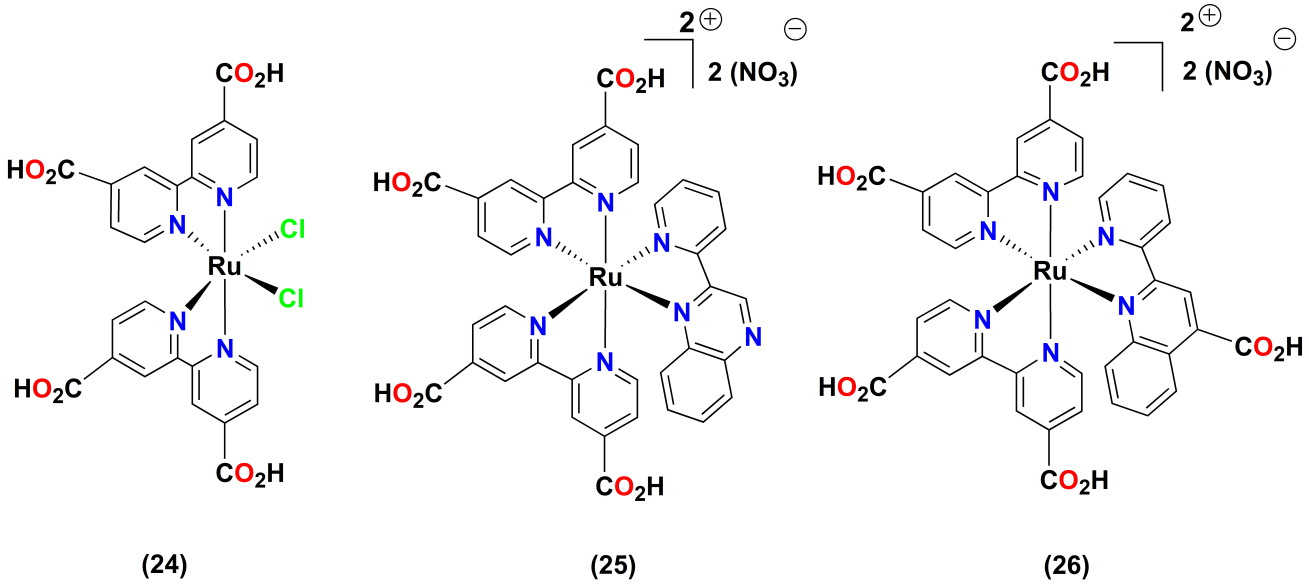
Besides the coordination compounds and organometallic complexes that have been reported so far, several other copper(I) [168], Ga(III) [168] , ruthenium(II)/(III) [189], rhodium(I)/(III) [168] and iridium (I)/(III)-based inhibitors [190] of the PAF-induced aggregation in both rabbit and human platelets *in-vitro*, in the nanomolar and sub-micromolar range have been investigated. Experiments on human platelet-rich plasma, in conditions closer to the *in-vivo* ones, were also performed for a series of copper(I) and rhodium(I) complexes, against other well-established platelet agonists like ADP and collagen.

To support our findings further theoretical docking calculations are required to test our hypothesis of the most potent inhibitor that fits within the binding site of PAFR. Provided that the X-ray crystal structure of PAFR in complex with SR27417 antagonist has been recently elucidated, these results would enable us to organize better and suggest better metal-based inhibitors in the future [191]. Overall, the above results highlight the increased impact of the vast area of metal-based coordination compounds that could potentially be tested as inhibitors against the PAF-induced biological activities, and subsequently for anti-cancer benefits. It has been demonstrated that co-administration of potent PAF inhibitors remarkably improves the pharmacological action of compounds with cytotoxic properties [33,34]. Therefore, the development of new compounds that display dual anti-cancer and anti-PAF activities can be considered as an interesting approach in the fight against cancer. Nevertheless, more studies are needed to evaluate their safety and efficacy, while *in-vivo* studies must be performed too in order to support the aforementioned promising *in-vitro* outcomes.

3.2 Natural Bioactives with Anti-PAF and Anti-Cancer Health Promoting Properties

Several natural bioactives have been found to affect the PAF/PAFR inflammatory pathway, with favorable anti-inflammatory health promoting properties against inflammation-related chronic disorders [32], including cancer, which have previously been extensively reviewed by Tsoupras *et al*. (2009) [2] and Lordan *et al*. (2019) [1]. In these previous reviews several natural bioactives with anti-PAF activity have been outlined. From the year of 1995 and the investigation of the Swedish fauna [192], to 2009's reviewing of anti-cancer properties of natural bioactives with anti-PAF properties [2] and 2013's natural PAFR antagonists review efforts [193], as well as 2019's anti-cancer dietary PAF-inhibitors potential elucidation [1], it is profound that there is a continuous assessment of anti-inflammatory natural bioactives for protection against PAF-related manifestations of cancer. In the present work the most recent outcomes on natural bioactives with both anti-PAF and anti-cancer health promoting properties are outlined and clarified.

For example, even though extensive research has been conducted in the anti-cancer properties of several phytochemicals that also possess anti-PAF properties, recent studies have outlined that bioactive phenolic compounds like resveratrol and flavonoids, demonstrate anti-inflammatory activities through the PAF/PAFR pathways and can reduce PAF-synthesis, leading to a decrease in the overall inflammatory response. The ability of these bioactive compounds to lower the levels and activity of



	24	25	26
IC_{50} (μM)	4.5	0.18	0.24

Fig. 4. Characteristic examples of synthetic metal-based complexes as inflammatory modulators with dual anti-PAF and anti-proliferative activities against cancer cells. IC_{50} values in μM concentrations against the PAF-induced aggregation of washed rabbit platelets are also presented.

thrombo-inflammatory mediators, namely PAF and thrombin, is rather promising against chronic diseases, including cancer [2,32,194–201]. A classic example is resveratrol with proven anti-cancer, anti-inflammation and anti-oxidant actions [202], normally found in apples, grapes, etc., with strong anti-PAF effects in platelets and an ability to modulate PAF-metabolism towards reduced PAF-levels, which further supports its anti-inflammatory potential [2,32,194–196,198,203,204]. Attention has also been given to resveratrol's derivatives. For example, an anti-proliferative and anti-PAF-induced platelet coagulation study took place with a di-acetylated derivative of resveratrol, where increased anti-platelet activity of diverse derivatives exhibiting different *in-vitro* anti-cancer effects were observed [205].

Other natural bioactives include andrographolide, α-bulnesene, kadsurenone, tussilagone, cinchonine, yangambin, piperine and cedrol, along with extracts from plants like *Urtica dioica*, piper species, pine pollen and extracts from marine plants, as well [123,193]. In Table 3 (Ref. [127,131,206–210]) and Fig. 5 many anti-cancer natural bioactives with anti-PAF and/or generally anti-inflammatory properties are further outlined, so as to clarify naturally-derived inhibitor's involvement and confirmed dual-action against PAF and/or cancer.

Such classic natural bioactives with anti-PAF and anti-cancer activity are represented clearly in the case of Ginkgolides. Their role as PAFR antagonists with anti-cancer effects, has been declared for quite some time [118,211,212]. In the last five, years the focus of research on these molecules has been shifted to the products of their aminolysis so as to obtain a potential enhancement of their anti-PAF activity [213]. A-Hederin and Kadsurenone have been investigated for several dual anti-PAF and anti-cancer effects with positive results (Table 3).

Other intercellular signaling pathways that involve anti-PAF action have also been proposed, including the MAPK's signaling pathway-related Solamargine [214], LC3-I and LC3-II-related Hederagenin [215,216], as well as Tagitinin C [215,217], Narirutin and possibly other flavonoids [215,218], which hold anti-cancer and anti-inflammatory potential when co-administered with traditional treatments. Whether their anti-inflammatory and anti-cancer responses could possibly be PAF/PAFR mediated should be further examined [215].

Likewise, Withaferin A, an equine known as a supplement under the name "*Ashwagandha*", promotes apoptosis of cancer cells when interacting with signaling pathways, like STAT and NF-κB [219] and has anti-proliferation, anti-migratory and mediatory roles on inflammation and angio-

Table 3. Characteristic studies assessing the anti-Cancer effects of Natural Bio-DAPAC-tives with anti-PAF properties.

Type of study – inflammatory signalling	Model	Study Design	Outcomes	Main Outcomes - Conclusions	Ref.
Clinical Trial	HCC patients.	● Daily administration of 5 g of curcumin, 50 mg of piperine, and 500 mg of taurine in a capsule.	● Increase in CD4, CD8, IL-2, IL-12, IFN-γ and decline in CD25, IL-6, VEGF-α, LDH, and AFP post capsule administration.	● Said capsule could show an immune-stimulating effect in HCC patients.	[207]
Clinical Trial	Chemotherapy patients.	● Administration of spirulina (*Arthrospira sp.*) to one group but not to the control group.	● The treated patients had a significantly lower rate of severe myelosuppression and less modification of the chemotherapy regimen was necessary. ● IgM level and CD8+ T cells increased in the treatment group, but decreased in the control group, after four chemotherapy cycles.	● Spirulina can act as an adjuvant to chemotherapy since it attenuates myelosuppression and helps immune function in patients with malignant tumors.	[208]
PAF/PAFR (*In-vivo*)	Nude mice bearing SKOV3 cells that were grown subcutaneously as tumor xenografts.	● Treatment of SKOV3-bearing mice with GB and examining its effect on tumor stemness.	● GB inhibited tumor growth, decreased the CSC percentage compared with the control group with no obvious side effects observed with higher recorded weights in the GB group and a decreased Ki67 and CD34 expression.	● GB can be used for weight control and as a way of inhibiting cell proliferation and angiogenesis in ovarian cancer cells *in-vivo*.	[127]
PAF/PAFR (*In-vitro*)	BC cell line: MDA-MB-231.	● Treatment of cells with PAF and with or without Kadsurenone. ● Co-culture of MDA-MB-231(PAF+) cells with RAW264.7 cells and treatment with Kadsurenone. ● Treatment of Mouse BMMs with Rank l and with or without Kadsurenone.	● Inhibition of PAF-induced BC cells migration and NF-κB activity, by Kadsurenone dose-dependently. ● Co-culture could promote osteoclast formation in the RAW264.7 cell line. ● Inhibition of osteoclast marker genes (*Ctsk*, *Trap*, *Nfatc1*) by Kadsurenone.	● Kadsurenone inhibits BC cells, and RANKL-induced osteoclastogenesis via NF-κB pathway.	[209]
STAT3 (*In-vivo*)	Hcclm3 cells *in-vivo* rat model.	● Stable Hcclm3-luciferase cells were injected intravenously, and PAF and/or α-Hederin were intervened by intraperitoneal injection.	● Phospho-STAT3 expression in metastatic tumor tissues of the PAF group was significantly higher than that of the metastasis control group, cotreatment groups with α-Hederin markedly decreased the expression of phospho-STAT3 in cancerous tissue. ● The PAF treatment group showed quick development of metastatic tumors while dramatically lower in co-treatment groups with α-Hederin.	● α-Hederin could suppress the PAF-promoted lung metastasis of HCC *in-vivo*.	[131]
In-vivo	BALB/c mice.	● Observation of tussilagone administration on AOM/DSS-induced colitis-associated colon cancer.	● Treatment diminished formation of colon tumors through downregulation of β-catenin expression, reduction of cell proliferation and evoking apoptosis.	● Tussilagone attenuates AOM/DSS-induced colon cancer evoking apoptosis in BALB/c mice.	[206]
Ex vivo & *in-vitro*	Prostate tissue after biopsy and prostate cell lines.	● Daily administration of resveratrol in a dietary-achievable way (5 mg) or pharmacological way (1 g).	● Resveratrol was undetectable in said tissue. Its metabolites although were in an accompanying *in-vitro* study did not consistently inhibit cell growth.	● Daily doses of Resveratrol less than 1 g may not have direct effects on the human prostate.	[210]

Abbreviations: Bio-DAPAC-tives, Bioactives with dual anti-PAF and anti-cancer activities; AFP, Alpha-Fetoprotein; GB, Ginkgolide B; BMMs, Bone Marrow Monocytes; AOM, Azoxymethane/DSS, Dextran Sulfate Sodium; HCC, Hepatocellular carcinoma; BC, Breast Cancer; IFN-γ, Interferon gamma; LDH, Lactate Dehydrogenase; AFP, alpha-fetoprotein.

genesis [220]. In addition, its safety has already been assured in many clinical trials [221]. Although Withaferin A has been reported to inhibit neutrophil migration towards PAF [222] and PAF activates neutrophils, it has not been proven whether its anti-cancer effects are mediated through PAF inhibition.

Less research has been done on apigenins making tumor xenografts more susceptible to doxorubicin [223], while apigenin-derived phyto-constituents of *A. elliptica* exhibit anti-inflammatory [224] and anti-PAF effects [225] as extracts. Piperlongumine has shown inhibition of PAF-induced platelet aggregation [226] and cytotoxicity for HCC, with its characteristics bringing about a way to synthesize instead of plant-extracting this inhibitor, so as to research its tumor targeting [227]. Moreover, *Carica papaya* leaf extracts as anti-cancer bioactives have already been reviewed [228], but a combined anti-PAF involvement of the included phyto-constituents, is yet to be examined. It is noted though that the mature leaf juice inhibits PAF, while it stabilizes and increases platelet counts of thrombocytopenic rats [229].

Curcumin affecting the NF-κB-related signaling, and the hydroxysafflor yellow A (HSYA), are natural bioactives posessing both anti-PAF and anti-cancer effects [215,230]. HSYA specifically, has been recognized as a great PAFR antagonist with an anti-inflammatory ability, strong enough to pose as a drug against bronchial asthma [231] and as a substantial anti-cancer agent. Indeed it is involved in the modulation of the immune microenvironment, as observed in an mice model for HCC, where HSYA was combined with cisplatin [232]. This study revealed that HSYA inhibited tumor growth without causing mice's weight loss, while cisplatin's adverse effects were questioned since it also caused tumor growth discontinuation along with mice's weight loss and reduced immunoreactivity [232].

Tusilagone, as shown in Table 3, has also been linked to attenuating inflammation-evoked carcinogenesis in cancer-colitis rat models [206]. Moreover it inhibited cancer cell proliferation and VEGF-induced angiogenesis as suggested from *in-vitro* and *in-vivo* experiments [233]. Tussilagone originates from the herb *Tussilago farfara* and exhibited antiproliferative and anti-inflammatory effects in breast cancer cell lines [234].

Furthermore, if inhibitory action against secreted PLA2-IIA as a component that precedes PAF production—via lysophosphotidate conversion—is considered, then anti-PAF phytochemicals like corosolic acid [235] and quercitrin [236] can become novel choices with both anti-inflammatory and anti-tumor effect in carcinoma-bearing and EAC-bearing mice, respectively.

Marine derived natural bioactives such as dietary omega-3 polyunsaturated fatty acids (n-3 PUFA) including docosahexaenoic acid (DHA), have also been found to possess both anti-PAF and anti-cancer properties [237]. For example, DHA has been linked to a noted phenotype differentiation in an eosinophilic leukemia (EoL-1) cell line assessment and a downregulation of sPLA2, PAFAH and *MYC* oncogene, with a subsequent upregulation of PAFR expression. Such a PAF/PAFR involvement should be further studied and utilized for the enhancement of an anti-proliferation action against EoL-1 leukemic cells [238]. Last but not least, extracts of marine algae like *Spirulina* possess anti-cancer effects and anti-PAF actions [239–241]. However, no follow-up study has been conducted yet, in order to correlate these benefits, especially *in-vivo* [240].

By using data acquired from the Cochrane Central Register of Controlled Trials (CENTRAL) all reported developments on clinical trials using all aforementioned natural anti-PAF and anti-cancer bioactives, were identified and reviewed. This was facilitated by using the NCT number of the clinical trials when available, or the main ID provided by the International Clinical Trials Registry Platform (ICTRP) Search Portal. For example, natural anti-PAF bioactives like Andrographolides, have been employed in studies as an adjuvant to drugs [242–244] including capecitabine for colorectal cancer patients (NCT01993472) without posted results. Cinchonine has been studied in a dietary trial of obese adults undergoing a low-calorie diet (Main ID: ISRCTN13055163) [245] but not in cancer patients.

Piperine has been studied as a biomarker/indicator of processed red meat consumption in randomized trials, but to the best of our knowledge it has not been correlated with cancer [246]. Other bioactives combinations, namely curcumin and taurine are investigates in a phase II clinical trial probing for potential stimulation effects on HCC patients as shown in Table 3 [207]. However, piperine (Main ID: EUCTR2016-004008-71-NL) [247] along with curcumin, have been shown to diminish tamoxifen and endoxifen pharmacokinetics in breast cancer patients, compromising research and calling for monitoring of intake [248].

As aforementioned, resveratrol, is one of the most studied natural bioactive phytochemicals in a plethora of clinical studies that in the past have already been linked to anti-cancer activities, e.g., evoking apoptosis of cervical cancer cell lines [249] and acting even as an adjuvant to cytotoxic drugs, like celecoxib protecting against breast cancer in rats, undergoing carcinogen administration [250]. In the last five years and focusing on cancer, a tendency to correlate resveratrol with prostate cancer is observed. Moreover, studies seem to focus on resveratrol's possible alleviating effects on cancer patients (Main ID: CTRI/2017/04/008376) [251], even as a way to attenuate toxicities on 5-Fluorouracil based chemotherapy recipients, in a Resveratrol-Copper state (Main ID: CTRI/2023/07/055750) [252]. As a well-known food supplement, resveratrol is currently being tested along with other safe molecules like aspirin and metformin, in their potential to prevent polyps' reformation and possibly bowel

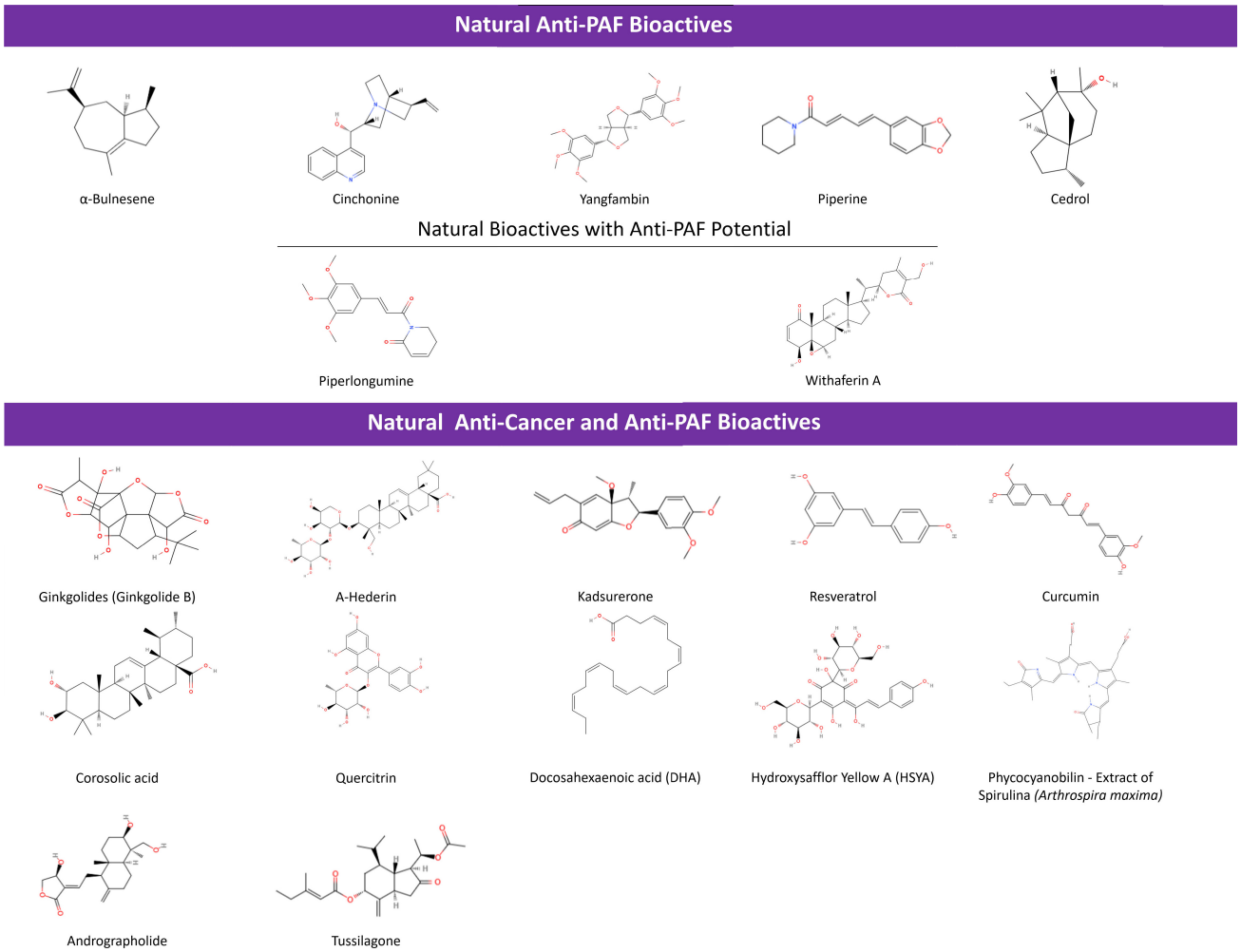


Fig. 5. Natural Bioactives with anti-PAF and anti-cancer activities.

cancer (Main ID: ISRCTN13526628) [253]. Its effect was also researched on breast cancer survivors along with an exercise regime (Main ID: RBR-87g6ny8) [254], on patients of oropharyngeal cancers undergoing chemo-radiotherapy looking for oral mucositis prevention activities (Main ID: CTRI/2019/06/019500) [255], on patients undergoing brain radiotherapy for observation of brain metastases of lung cancer (Main ID: CTRI/2020/09/027794) [256].

Curcumin has been extensively reviewed for its therapeutic roles in the past [257]. A placebo-controlled clinical trial with curcumin administration was conducted in patients with colorectal cancer undergoing chemotherapy and serum inflammatory cytokines and quality of life were assessed (Main ID: IRCT20080901001165N43) [258].

DHA in the last 5 years has been tested on breast cancers and colon cancer as well. In the placebo controlled trial women with a history of breast cancer were administered with a daily dose of DHA (1000 mg). While higher levels of omega-3 fatty acids were found in the blood of the intervention group, TNF-α, biomarkers and transcriptome behavior on breast tissues were not reduced [259], pointing to the need to test different DHA doses in future studies. Later, the combination of chemotherapy and DHA was studied in a double-blind, phase II, randomized controlled trial [260], for its comparison to alone cytotoxic treatment in breast cancer patients. Lastly, possible positive effects of treatment with DHA among arginine and eicosapentaenoic acid (EPA) were investigates before surgery on colon cancer patients (Main ID: UMIN000031984) [261].

One important and thoroughly studied natural inhibitor is Phycocyanobilin, the extract of Spirulina (Arthrospira maxima), with strong anti-PAF properties [240]. Dietary Spirulina can be co-administered with cytotoxic anti-cancer drugs to minimize myelosuppression [208]. Concordantly, it has been tested for neurotoxicity in patients with gastrointestinal cancer undergoing chemotherapy, with undisclosed results [262].

As far as Tussilagone [206], α-Bulnesene, Yangambin, Cedrol, Ginkgolides, A-Hederin, Kadsurenone, Corosolic acid, Quercitrin, and Hydroxysafflor Yellow A (HSYA) are concerned, they have not been tested in clinical trials to the best of our knowledge.

3.3 Anti-Cancer Activity of Dietary Patterns Rich in Anti-PAF Dietary Natural Bioactives

Healthy dietary patterns like MD that are rich in anti-PAF natural dietary bioactives, have shown benefits against inflammation-related chronic disorders, including cancer [1,2,32]. The beneficial impact of a Mediterranean-based dietary lifestyle has been intensively studied in several chronic diseases—directly or indirectly connected to inflammation, that are often fatal—including: CVD [263], obesity [264,265], heart failure [266], diabetes (type 1 & 2) [267–269], diabetic retinopathy [270], metabolic syndrome [271–273], frailty risk [274], Alzheimer's disease, brain atrophy, cognitive impairment and dementia [275–279], and plus, asthma [280–282], allergies [280,283], hepatic fibrosis and non-alcoholic fatty liver disease [284,285], inflammatory bowel disease [286,287], autoimmune diseases such as rheumatoid arthritis [288,289], lupus [290], or Hashimoto's disease [291] and of course—our matter of interest, cancer and other subsequent manifestations [32].

The correlation between dietary patterns and cancer, has been vigorously studied and as a result, MD, which is rich in cereals, olive oil, fruits, vegetables, fish, wine and low in saturated fats and animal-related food, is believed to protect against several cancer types and even premature mortality in general [1,292–294]. MD's profile is rich in many natural antioxidants, bio-functional polar lipids and bioactives that have been proved to own anti-PAF activities, however, it is yet uncertain whether the link between MD and PAF is due to the reduction of underlying inflammation caused by an antioxidative diet or if antioxidants directly affect PAF's metabolism [1,295]. Interestingly, the antioxidant capacity of the diet has been negatively related to PAF levels in a cross-sectional study in healthy subjects [296]. Foods included in the MD diet pyramid and their derivatives are indeed rich in anti-PAF bioactives as concluded in several clinical trials.

The results of a meta-analysis, indicated that MD is able to potentially reduce inflammation and improve the endothelial function [297], while the MD lifestyle that is comprised of high amounts of PAF-inhibitory components, is also associated with cancer prevention [298]. Although there is scientific evidence concerning the vital preventative and protective role of MD against cancer [299], it has yet to be clarified through more comprehended data, if present health-related conditions and disorders like CVD or obesity in cancer patients, are favoring or discouraging the efficacy of dietary PAF inhibitors towards PAF activity and cancer progression [1].

Global research towards MD-cancer relation has gathered a more targeted interest over the past decade (2012–2022), where the total number of studies surpassed 200, in 2021 due to cancer already being a hotspot of research [300]. Clustering results of many conducted studies suggest that the MD is highly correlated to reduced risk of overall cancer mortality, as well as of several types of cancer including head, neck, colorectal, breast, gastric, liver, stomach, pancreatic and prostate cancer, due to this diet's high nutritional intake [280,301].

MD is also able to reportedly modulate the diversity of the gut microbiota, which also seem to contribute in the prevention of several cancer types like colorectal and breast cancer, by mainly reducing inflammation [300,302]. Olive oil MD-derived polyphenols own beneficial effects towards cancer and tumorigenesis, because of their interaction with the gut microbiota, their regulative role that transforms it so as to include more protective bacteria and their contained bioactive metabolites [300]. Olive oil and its polyphenols as reported, may lead to 30% lower probability of digestive cancer occurrence [303].

The European Prospective Investigation into Cancer and Nutrition (EPIC-Europe) is a long-term, large-scale collaborative project that studies different populations from countries across Europe to investigate the relationships between diet, nutrition, lifestyle, and environmental factors, and the incidence of cancer and other chronic diseases. It is one of the largest cohort studies in the world, with more than half a million participants recruited across 10 countries in western Europe. EPIC-Europe was launched in the 1990s and has been going on for more than 30 years. The multicenter EPIC study found that the highest-recorded MD score was related to 7% reduction in total cancer risk in both male and female genders [304].

Limited yet significant evidence support MD's efficacy—with no fat intake restriction—in decreasing the possibility of cancer-related incidents like CVDs, breast cancer and type 2 diabetes mellitus [305,306], while the adoption of such dietary pattern may contribute to heart failure's prevention [307]. Specifically, regarding breast cancer (BC), consuming MD foods before its' diagnosis, may improve long-term prognosis, especially after menopause and BC metastasis [308,309]. Also, lower risk rates of digestive tract cancers [310], obesity-enhanced cancer [311], metabolic syndrome and cancer longevity [272,306], have been proved and support MDs overall efficiency. All of these studies, conclude that the natural bioactives contained in a MD plan, are anti-PAF and anti-inflammatory agents able to prevent cancer, protect cancer patients from further metastasis progression and impede several proinflammatory mechanisms (Table 4, Ref. [312–336]) [1,32,295,300]. Overall, following a MD pattern rich in anti-PAF bioactives, consumers may achieve more protection against overall cancer occurrence and thus, longevity.

In contrast, adoption of a Western diet-related foods, including ultra-processed [337,338] food sources, increased 23% head and neck, 24% esophageal adenocarcinoma cancer [339] and 5% BC risk [340]. It is noted that the consumption of ultra-processed foods is inversely related to a Mediterranean dietary pattern [341]. Furthermore, a higher possibility of colorectal cancer through red and processed meat consumption, was also associated with Westernization

Table 4. Analytical study designs of dietary Bio-DAPAC-tives in cancer clinical trials.

Study Name	Study Design	Origin	Patients/Controls (n)	Subjects (n)	Type of Cancer	Intervention Details	Control Details	Results	Ref.
Curcumin									
Belcaro *et al*., 2014	60 days	Italy	● Chemotherapy: - 40 curcumin - 38 control ● Radiotherapy: - 40 curcumin - 40 control	● Chemotherapy: - 20 curcumin - 20 control ● Radiotherapy: ● 18 curcumin ● 21 control	● Chemotherapy: colon/rectum, liver or kidney, stomach, lung, female genital system including the ovaries, or haematological malignancies ● Radiotherapy: colon/rectum, liver or kidney, stomach, or lungs	● 500 mg Meriva [100 mg Curcuminoids (ratio curcumin:demethoxycurcumin: bis-demethoxycurcumin 33:8:1)], 200 mg soy lecithin and 200 mg microcrystalline cellulose, 1 × 3 times per day after meal	● Comparable tablet 1 × 3 times per day after meal	● ↓ Symptoms (Nausea and vomiting, diarrhea/constipation, fatigue, malnutrition/weight loss, memory/cognitive function impairment, etc.)	[312]
Chaiworramukkul *et al*., 2022	8 weeks	Thailand	● 17 curcumin ● 16 Placebo	● 12 curcumin ● 14 Placebo	● Lung, head and neck, other gastroenterology, colorectal, breast, other (with cancer anorexia–cachexia syndrome)	● 800 mg curcumin × 2 (Each capsule contained 240 mg of curcuminoids)	● Capsule with cornstarch	● No differences in body composition in cancer patients with cancer anorexia–cachexia syndrome ● Slower progression of hand-grip muscle strength loss, basal metabolic rate	[313]
Hidayat *et al*., 2021	7 days	Indonesia	● 20 curcumin and radiation ● 20 placebo and radiation	● NA	● Cervical cancer	● 4 g curcumin/day ● from 7 days before the radiotherapy until the day of radiotherapy	● Vitamin B complex	● Radiation therapy was more successful with curcumin co-administration ● Survivin† levels were significantly different with curcumin administration	[314]
Hejazi *et al*., 2016	9 weeks	Iran	● 20 curcumin ● 20 placebo ● (All patients were receiving radiotherapy)	● 40	● Prostate cancer	● 3 grams of curcumin (2 capsules with each meal) ● Capsule of 440 mg curcumin (curcumin of 347 mg, desmethoxycurcumin of 84 mg, and bisdesmethoxycurcumin of 9 mg) and essential oil of turmeric of 38 mg	● 500 mg Roasted Rice flour (2 capsules with each meal)	● ↑ TAC ● ↓ SOD	[315]
Ramezani *et al*., 2023	21 days	Iran	● 13 curcumin mouthwash ● 12 curcumin capsules ● 12 placebo mouthwash	● 23	● Head and neck cancer	● Mouthwash: 100 mg of curcumin powder, freshly prepared solution (10 mL of freshly prepared mouthwashes × 3 times a day) ● Sinacurcumin soft gel containing 40 mg curcuminoids as nano – micelles (SinaCurcumin®40) one capsule per day	● Placebo mouthwash	● ↓ Pain and burning related to oral mucositis ● Ns difference between oral or topical forms of curcumin	[316]

Table 4. Continued.

Study Name	Study Design	Origin	Patients/Controls (n)	Subjects (n)	Type of Cancer	Intervention Details	Control Details	Results	Ref.
Howells *et al*., 2019	Once every 2 weeks for $\leq$12 cycles or until patient progression, unacceptable toxicity, death, or withdrawal	United Kingdom	• 18 curcumin • 9 control	• NA	• Metastatic colorectal cancer	• FOLFOX $\pm$ bevacizumab plus 2 g oral Curcumin C3 Complex/d • ($\sim$80% curcumin and 20% demethoxycurcumin and bisdemethoxycurcumin)	• Standard-of-care chemotherapy (FOLFOX $\pm$ bevacizumab)	• $\uparrow$ overall survival in curcumin group • No difference in progression-free survival • No difference in quality of life or neurotoxicity • No changes in CXCL1	[317]
Talakesh *et al*., 2022	5 days per week for 5 weeks: the curcumin was consumed up to two weeks after the end of treatment	Iran	• 21 nano-curcumin • 21 control	• 0	• Breast cancer under radiotherapy	• 80 mg per day nano-curcumin capsules (twice a day)	• Soybean oil	• No difference in severity of radiation-induced skin reactions at 0–6 weeks • $\downarrow$ Severity of radiation-induced skin reactions at week 7 • $\downarrow$ Self-reported pain	[318]
Resveratrol									
van Die *et al*., 2017	12 weeks	Australia	• 9 supplement • 11 control	• 22	• Biochemically recurrent prostate cancer	• 2 tablets $\times$ 2 daily + 2 capsules $\times$ 2 daily broccoli • Turmeric (*Curcuma longa*) rhizome extract, 25:1, standardized for curcumin 95%, assay 95–105% total curcuminoids; curcumin 100 mg (400 mg/day) • Resveratrol (*Polygonum cuspidatum*) extract dry concentrate, 100:1, containing min 50% resveratrol, 30 mg (120 mg/day) • Green tea (*Camellia sinensis*) leaf dry concentrate, 25:1, containing min 50% polyphenols; catechins 100 mg (400 mg/day) • Broccoli (*Brassica oleracea var. italica*) sprout concentrate 20:1, equivalent to fresh sprouts 2000 mg (8 g/day)	• Powdered green oats, aerial parts (*Avena sativa, L., Graminaceae family*)	• Good adherence to study protocol and good tolerance of the supplements • No difference in prostate symptoms, quality of life, anxiety, and depression	[319]
Howells *et al*., 2011	10–21 days	USA	• 6 resveratrol • 3 control	• NA	• Stage IV • Colorectal Cancer and Hepatic Metastases	• SRT501 (micronized resveratrol)	• Titanium Dioxide	• SRT501 was well tolerated • $\uparrow$ cleaved caspase-3 (marker of apoptosis) by 39% in malignant hepatic tissue	[320]

Table 4. Continued.

Study Name	Study Design	Origin	Patients/Controls (n)	Subjects (n)	Type of Cancer	Intervention Details	Control Details	Results	Ref.
Quercetin									
Henning *et al*., 2020	4 weeks	USA	● 15 Quercetin ● 16 control	● 31	● Prostate cancer	● 1 gram of green tea extract ● (830 mg of green tea polyphenols) + 800 mg of Quercetin ● (2) two capsules of green tea extract ● (Tegreen 97) with one capsule of Quercetin (N = 15) or (2) two capsules of green tea extract	● Green tea extract + one capsule of placebo	● No effect on epigallocatechin gallate and epicatechin gallate concentrations nor methylated green tea polyphenols in prostate tissue ● Quercetin may affect green tea polyphenols metabolism (glucuronidation) as evidenced by decreased urinary levels of epigallocatechin and 4′-methyl epigallocatechin	[321]
Kooshyar *et al*., 2017	4 weeks	Iran	● 10 intervention ● 10 control	● NA	● On Chemotherapy	● Quercetin Hydrate (Sigma–Aldrich Co; St Louis, MO, USA), (250 mg × 2 per day)	● Lactose Capsule	● ↓ Mucositis incidence in the quercetin group, but mucositis was more severe in the intervention group, possibly due to worse oral health status	[322]
Buonerba *et al*., 2018	81 days	Italy	● 12 patients	● 11	● Kidney Cancer	● 225 mg Isoquercetin (IQC-950AN) + 55.8 mg ascorbic acid + 4.5 mg nicotinic acid (×2 per day – no interruption) in the 1st 6-patients - Isoquercetin was delivered conjointly with sunitinib (initial daily dose: 50 mg) for: - Two (4:2) or - Four (2:1) sunitinib cycles	● 450 mg Isoquercetin (IQC-950AN) + 111.6 mg ascorbic acid + 9 mg nicotinic acid (×2 per day – no interruption) in the 2st 6-patients - Isoquercetin was delivered conjointly with sunitinib (initial daily dose: 50 mg) for: - Two (4:2) or - Four (2:1) sunitinib cycles	● Isoquercetin administered along with Vitamin C and B3, displayed excellent safety, patient compliance and encouraging activity in terms of obvious improvement of fatigue, and possibly other adverse events (e.g., hand and foot syndrome) associated with sunitinib	[323]

Table 4. Continued.

Study Name	Study Design	Origin	Patients/Controls (n)	Subjects (n)	Type of Cancer	Intervention Details	Control Details	Results	Ref.
Zwicker *et al*., 2019	56 days	USA	● 28 isoquercetin at 500 mg ● 29 isoquercetin at 1000 mg	● 34	● Cancer patients at high risk for thrombosis, pancreatic, non–small cell lung, and colorectal malignancies	● 500 mg isoquercetin	● 1000 mg isoquercetin	● 1000 mg isoquercetin ↓ 21.9% plasma D-dimer (There were no primary venous thromboembolism events or major hemorrhages observed) ● Isoquercetin ↑ protein disulfide isomerase inhibitory activity in plasma ● ↓ Platelet-dependent thrombin generation ● ↓ Soluble P selectin (1000 mg isoquercetin dose)	[324]
Mulholland *et al*., 2001	One intravenous treatment and one oral treatment seperated by 14 days (If the treatment was found beneficial to patients, they continued to have QC12 intravenous every 14 days, up to maximum 6 treatments	Netherlands	● 6 patients ● All oral and intravenous received: - 400 mg of QC12 (equivalent to 298 mg of quercetin), orally and on day 1 and intravenously (i.v.) in normal saline on day 14	● 3	● Two had colorectal cancer with liver metastases, two had hepatocellular carcinoma, one had pelvic reccurence of leiomyosarcoma and one had thoracic mesothelioma	● Oral QC12 was given at a fixed dose of: - 400 mg + 100 mL made up fresh orange juice - Patients had fasted from the previous evening from 11 PM	● Intravenous QC12 was also at a fixed dose of 400 mg, dissolved in 40 mL of normal saline as a five-minute infusion.	● After the oral administration of QCl2, inability to detect QC12 or quercetin in plasma ● After i.v. administration, peak plasma conc. of QC12 (108.7 ± 41.67 uM) were detected. ● A two-compartment model with mean ti/2a of 0.31 ± 0.27 h and mean t|/2P of 0.86 ± 0.78 h best described the conc.-time curves for QC12 (mean AUC = 44.54 ± 13.0) uM.hour and mean volume of distribution (Vd) = 10.0 ± 6.2 litres ● Quercetin was found in all patients following i.v. infusion of QC12, with peak levels of quercetin 19.9 ± 11.8 uM ● The relative bioavailability of quercetin: estimated ∼20%–25% quercetin released from QC12 ● QC12 is not orally bioavailable. This water-soluble prodrug warrants further clinical investigation; starting with a formal phase I, IV, dose-escalation study	[325]

Table 4. Continued.

Study Name	Study Design	Origin	Patients/Controls (n)	Subjects (n)	Type of Cancer	Intervention Details	Control Details	Results	Ref.
Lee *et al*., 2015	At least 3 weeks (21–61 days)	South Korea	• 10 intervention • 10 remission diet	• NA	• Various types of cancer	• Low glycemic, low fat, and high plant protein diet; the intervention group had an additional 0.5 servings of protein. Based on clinical values, additional amounts of garlic, onion, tomato, shiitake, rice bran, kale, blueberry, pineapples, and/or turmeric powder were provided in regular meals	• Low glycemic, low fat, and high plant protein diet	• ↑ vitamin A, vitamin C, vitamin E and selenium intake • ↓ D-dimer in both groups • ↓ Reactive oxygen metabolites in the remission diet • ↑ Albumin and an increased tendency in cytotoxicity in the intervention group were observed • No change in CRP, ferritin, fibrinogen, glucose, and IGF-1	[326]
Ginkgolide B									
Dias *et al*., 2015	Followed up for Approxim tly 90 days	Brazil	• 8 ginkgo biloba extract • 7 control	• NA	• Various soft tissue neoplasms, including ovarian, testicular, cervical, head and neck, lung and bladder cancer under cisplatin treatment	• Ginkgo biloba extract 761 (120 mg × 2 per day)	• Placebo (×2 per day)	• The control group had smaller distortion product otoacoustic emissions mean amplitudes and smaller signal/noise ratio than the intervention group	[327]
Docosahexaenoic Acid (DHA)									
Pratt *et al*., 2002	14 days	USA – Canada	• 13 fish oil • 10 placebo	• 18	• Various types of cancer	• Fish (Eicosapentaenoic acid, and DHA) • 1 g Gelatin capsules containing fish oil (180 mg EPA and 120 mg DHA), Banner Pharmacaps, Olds, AB, Canada) Capsules orally each day	• Placebo (olive oil)	• ↑ EPA and DHA in plasma but not neutrophil phospholipids • ↓ 20:4 n-6 in neutrophil phosphatidylinositol after fish oil • Change in body weight was related to increases in plasma EPA	[328]
Stephenson *et al*., 2013	72-hour infusion	United Kingdom	• 9 treatment • 11 control	• 9	• Hepatic Colorectal Metastases	• Total Parenteral Nutrition with PUFAs • 2000 mL Nutriflex basal® (B Braun, Melsungen, Germany) compounded with 500 mL Lipidem® 20% (B Braun) in the treatment group • Lipidem® will typically contain about 1.25 g EPA plus DHA (0.74 g EPA and 0.51 g DHA)	• 2000 mL Nutriflex basal® (B Braun, Melsungen, Germany) and 500 mL Lipofundin® MCT 20% (B Braun)	• ↑ plasma PC EPA and DHA and erythrocyte EPA • ↓ plasma PC and erythrocyte linoleic acid • Plasma PC and erythrocyte EPA and linoleic acid all returned to baseline levels after the 5–12-day washout • Plasma PC DHA remained elevated after washout	[329]

Table 4. Continued.

Study Name	Study Design	Origin	Patients/Controls (n)	Subjects (n)	Type of Cancer	Intervention Details	Control Details	Results	Ref.
Sorensen *et al*., 2014	7 days before and 7 days after surgery	Sweden	● 65 n-3 ● 64 control	● 80	● Colorectal Cancer	● 2 g EPA and 1 g DHA per day ● Enriched oral nutritional supplement (Supportan, 200 mL, 1 × 2)	● Standard oral nutritional supplement	● Mo difference in infectious or non-infectious postoperative complications ● ↑ granulocyte levels of EPA, DHA and docosapentaenoic acid (DPA) ● ↓ Granulocyte levels of arachidonic acid	[330]
Fietkau *et al*., 2013	Maximum of 14 weeks	Germany	● 55 experimental group ● 56 control group	● 93	Head, Neck and Esophageal Tumors	● 2.0 g EPA and 0.85 g DHA-enriched oral nutritional supplement (Supportan, 500 mL)	● Standard oral nutritional supplement ● (Fresubin Energy Fibre)	● The intervention group lost only 0.82 ± 0.64 kg of body cell mass vs 2.82 ± 0.77 kg ● Improvements in the subjective global assessment score	[331]
Heller *et al*., 2004	5 days post-operative	Germany	● 24 Soybean + Fish oil ● 20 soybean oil	● 32	● Gastrointestinal Tract or Pancreatic Cancer	● Total parenteral nutrition supplemented with a combination of fish oil (0.2 g/kg) and soybean oil (0.8 g/kg)	● Total parenteral nutrition with soybean oil (1.0 g/kg)	● ↓ aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and lipase in the fish oil group vs soybean oil ● ↓ length of stay in patients with IL-6/IL-10 ratio >8 (trend) ● No weight loss in the fish oil group	[332]
Chagas *et al*., 2017	9 weeks	Brazil – UK	● 9 supplementation ● 13 control	● 8	● Leukemia or Lymphoma	● fish oil capsules (2 g/day) (367 mg EPA and 243 mg DHA)	● Control	● ↑ plasma EPA and DHA ● ↓ CRP, CRP/albumin ● ↑ overall long-term survival (465 days after the start of the chemotherapy)	[333]
Sorensen *et al*., 2014	7 days	Denmark	● 21 intervention ● 19 Control	● 27	● Colorectal Cancer	● Oral nutritional supplement (200 mL × 2) + fish oil (2.0 g of EPA and 1.0 g of DHA per day)	● Oral nutritional supplement (200 mL × 2).	● ↑ EPA in colonic mucosal and muscular layer ● ↑ total n-3 FA (EPA+DPAn-3+DHA) in the colonic mucosa ● No difference in DHA and DPA in the colonic muscular layer	[330]

Table 4. Continued.

Study Name	Study Design	Origin	Patients/Controls (n)	Subjects (n)	Type of Cancer	Intervention Details	Control Details	Results	Ref.
Mocellin *et al*., 2013	9 weeks	Brazil	● 6 Fish oil ● 5 Control	● 6	● Colorectal Cancer	● 2 g/day of fish oil (600 mg/day of EPA and DHA) (4 capsules/day of fish oil)	● Control	● No difference in plasma TNF-α, IL- 1b, IL-10 IL-17A, and albumin ● ↓ C-reactive protein ● ↑ Plasma EPA and DHA ● ↓ Plasma arachidonic acid	[334]
Arsic *et al*., 2023	12 weeks	Serbia	● 14 Fish oil + Primrose oil ● 15 Control	● 0	● Breast Cancer under chemotherapy	● 2 gel capsules of fish oil and 3 gel capsules of primrose oil (400 mg EPA, 600 mg DHA, and 351 mg gamma-Linolenic acid)	● 5 g of mineral oil	● ↑ DPA, DHA, total n-3, vaccenic acid ● ↓ n-6/n-3 ratio ● No difference in IL-8, IL-10, TNF-α ● ↓ IL-6	[335]
Laviano *et al*., 2020	12 weeks	16 sites across Four countries (Croatia, Italy, Slovakia, and Sweden)	● 26 Oral nutritional supplements with EPA, DHA, vitamin D ● 29 Isocaloric	● 17	● Non-Small-Cell Lung Cancer	● Oral nutritional supplement (200 kcal; 10 g whey protein concentrate; 11 g fat including 1200 mg DHA 800 mg EPA in fish oil; 20 g carbohydrate and 25-hydroxy-vitamin D3 per 200 mL)	● Oral nutritional supplement (200 kcal; 6 g milk protein; 11 g fat and sunflower oil) (no EPA, DHA - vitamin D)	● ↓ Adverse effects ● ↓ Cases of neutropenia (0 vs. 4) ● ↓ Deaths by 1-year post-baseline	[336]

↑, increase; ↓, reduction. **Abbreviations**: Bio-DAPAC-tives, Bioactives with dual anti-PAF and anti-cancer activities; Ns, Non-significant; †survivin: an anti-apoptotic protein implicated in cell division and apoptosis inhibition; CXCL, Chemokine (C-X-C motif) Ligand; FOLFOX, Folinic Acid, Fluorouracil and Oxaliplatin; DHA, Docosahexaenoic; EPA, Eicosatetraenoic; HR, Hazard Ratio; NA, Not Available; SOD, Superoxide Dismutase; TAC, Total Antioxidant Capacity; CRP, C reactive protein.

of traditional food patterns, in contrast to the benefits of MD patterns that includes healthy foods rich in anti-PAF bioactives, such as oily fish, olive oil, fruits and vegetables [32,303,342]. It is therefore clear, that Westernization is favoring chronic cancer diseases, while Mediterranean and Nordic diets [343], with their PAF-inhibitors and anti-inflammatory mechanisms, may in fact function against their progression [1,32].

4. Concluding Remarks: Future Perspectives, Research Gaps and Limitations

The initial discovery, followed by the structural identification of PAF [76], notably increased research interest about its function in both health and disease. After thorough research and several clinical trials, PAF was indisputably involved in many pathophysiological states, and hence, research and design models on several PAF-inhibitors was and is still conducted. The focus of our study was shifted towards a thorough re-assessment of PAF's role in inflammatory signaling implicated in cancer development, progression and metastasis, as well as on the recent findings related to potent anti-PAF and anti-cancer inhibitors and their potential associations with cancer treatment strategies. Emphasis was given mainly to both natural and synthetic bioactives that possess a dual anti-PAF and anti-cancer potential, as shown not only with *in-vitro* and *ex-vivo* studies, but also by *in-vivo* studies and clinical trials. Last but not least, the potential of healthy dietary patterns containing anti-PAF natural compounds (such as MD) to act against cancer was discussed.

More specifically, in the present work, the axis of pathological inflammation to tumor-related angiogenesis and metastasis via PAF, facilitating cancer-related inflammation (CRI) was outlined. Based on these outcomes, it is evident that PAF and its inflammatory signaling can pose as therapeutic targets against neoangiogenesis and metastasis. PAF is an important inflammatory mediator linked to numerous intracellular signaling pathways—with the developments of NF-κB special role emphasized and presented distinctly. Dual cancer-promoting and anti-cancer actions of NF-κB are observed in different types of cancers, leading to either upregulation or downregulation of PAF, its G-protein coupled PAFR and its metabolism and metabolites.

NF-κB and PAF through their dual role may also interact with chemotherapy drugs. For example, PAF is excreted as a result of cytotoxic drug administration, facilitating the idea that anti-PAF action and PAF-inhibitors may be vital as an adjuvant strategy to traditional drugs in certain types of malignancy [147]. However, although PAF was recently proposed as a cancer biomarker [1], clinical trials have not yet fully clarified the effectiveness of PAFR antagonists as anti-inflammatory and anti-cancer treatment methods, a fact pointing to a research gap and posing a challenge for future research [76]. Creating research interest in dual anti-cancer and anti-PAF components design, development and applications—as represented by not only traditional synthetic, natural and dietary bioactives' research, but also by the synthesis of novel organometallic complexes as well—is a promising research area.

Our focus on natural anti-PAF bioactives and applied dietary consumed PAF agonists and PAFR antagonists [1,2], based on current trends in clinical trials, is mainly focused on previously studied bioactives against cancer research. The need to create a clinical understanding of anti-cancer action via anti-PAF strategies is now evident, as numerous *in-vitro* studies exist, but much less *in-vivo* studies have been performed, especially in patients with cancer. The limitation of the presented studies, is their inability to simulate the effects of the complex organ systems on PAF-related mainfestations. It seems that several studies based on animal models used for *in-vivo* applications, oftentimes with xerograph methodology, could be swapped to a more substantial portion of *ex-vivo* studies and clinical trials, for more reliable results. Such study designs are nonetheless highly significant in facilitating pre-clinical and pre-mature understandings and guiding future research.

Based on the presented outcomes on cancer patients with interventions of natural bioactives having anti-PAF activity, it was clear that the majority studies were focused on well-established anti-inflammatory bioactives like curcumin, piperine, resveratrol and DHA. Other strong anti-PAF natural bioactives like the bio-functional anti-inflammatory and antithrombotic dietary polar lipids may worth being studied in cancer clinical trials, since they have previously shown strong potential in other inflammation-related conditions involving endothelial dysfunction, such as atherosclerosis, CVD and neurodegenerative disorders, in a recently observed synergistic action between polar lipids derived from several MD sources, while when such polar lipids were infused with phenolics as ingredients in other foods they provided to the new products both antioxidant and anti-inflammatory functional health promoting properties [344–346]. Such a direction is also supported by the benefits of healthy dietary patterns like MD, that are rich in several bioactives with anti-PAF and anti-cancer potential and have been linked to disease prevention, higher longevity and quality of life [1,2,32,294]. A MD-based lifestyle, holds great prospects against cancer occurrence of various cancer types and progression, while clinically confirmed anti-PAF activity of many MD constituents, partially validates their anti-cancer activity as well [32,294,347].

Dietary PAF-antagonists, included in MD, mainly in olive oil and its derivatives, but also in fruits, vegetables, dairy, fish and other healthy foods, have great anti-inflammatory, anti-thrombotic, and thus, cardioprotective and anti-cancer potential [32,347]. Bio-functional polar lipids of such foods, due to their ability to both inhibit PAF and modulate its metabolism—mainly studied in *in-vitro* and *ex-vivo* setting, but also trialed *in-vivo* in animals and humans seem to possess great potential against chronic dis-

eases. Similar studies however, have not been conducted yet in cancer patients. Thus further investigation upon their daily consumption by cancer patients is needed. Nevertheless, it should also be stressed out that the potential of some of these dietary constituents is limited to their realistic amount consumed through one's diet versus the amounts tested in *in-vitro* studies. For example, resveratrol under a certain dosage relevant to that consumed through diet may not portray any significant anti-cancer behavior. It seems that the synergy of all the bio-functional compounds present in foods of MD, such as the anti-PAF bioactive polar lipids, several phytochemicals, n-3 PUFA, terpenoids, alkaloids, etc., is also important for the protective effects of this dietary lifestyle.

The collecting data of the current status knowledge, on PAF's role in cancer remediation efforts, holds much research interest and exciting potential. Taking into account the beneficial effects of healthy diets against inflammation and consecutively disease prevention, it seems that anti-PAF based anti-inflammatory approaches can contribute in the fight against cancer. Research advances on specific dietary interventions as well as the development of targeted nutraceuticals or novel synthetic anti-PAF compounds with anti-cancer potential may contribute to cancer prevention.

Author Contributions

Conceptualization, AT, AP and CAD; writing—original draft preparation, AT, TA, MAF and AP; writing—review and editing, AT, TA, MAF, AP, PD and CAD; collection of literature and interpretation of its data, AT, TA, and MAF (contributed in all text and tables), while PD, IT and MK contributed on the revision of Section 3.3, and on the preparation and creation of Table 4; drawing of figures, AT, TA and MAF draw Figures 1–3 and 5), while AP draw Figure 4; visualization, AT, AP and CAD; supervision, AT; project administration, AT, AP and CAD; Funding, AP and CAD. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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