The potential role of dietary platelet-activating factor inhibitors in cancer prevention and treatment

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Abstract

Cancer is the second leading cause of mortality worldwide. The role of unresolved inflammation in cancer progression and metastasis is well established. Platelet-activating factor (PAF) is a key proinflammatory mediator in the initiation and progression of cancer. Evidence suggests that PAF is integral to the suppression of the immune system and the promotion of metastasis and tumor growth by altering the local angiogenic and cytokine networks. Interactions between PAF and its receptor may play a key role in various digestive, skin, and hormone-dependent cancers. Diet plays a critical role in the prevention of cancer and its treatment. Research indicates that the Mediterranean diet may reduce the incidence of several cancers in which dietary PAF inhibitors may in part play a role. Dietary PAF inhibitors such as polar lipids have demonstrated inhibitory effects against the physiological actions of PAF in

Abbreviations used: bFGF, basic fibroblast growth factor; CVD, cardiovascular diseases; COX, cyclooxygenases; ECM, extracellular matrix; ICAM, intercellular adhesion molecule; iNOS, inducible nitric oxide synthase; LPCAT, lysophosphatidylcholine acyltransferase; Lyso-PAF-AT, lyso-PAF-acetyltransferase; MMP, matrix metalloproteinase; PAF, platelet-activating factor; PAF-AH, platelet-activating factor-acetylhydrolase; PAF-CPT, 1-alkyl-2-acetyl-sn-glycerol-cholinephosphotransferase; PAF-R, platelet-activating factor-receptor; PLA₂, phospholipase A₂; ROS, reactive oxygen species; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

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cancer and other chronic inflammatory conditions *in vitro* and *in vivo*. In addition, experimental models of radiotherapy and chemotherapy demonstrate that inhibition of PAF as adjuvant therapy may lead to more favorable outcomes. Although promising, there is limited evidence on the potential benefits of dietary PAF inhibitors on cancer prevention or treatment. Therefore, further extensive research is required to assess the effects of various dietary factors and PAF inhibitors and to elucidate the mechanisms that play a role in preventing cancer progression and metastasis at a molecular level.

Keywords: nutrition; cancer, platelet-activating factor; inflammation; metastasis; angiogenesis; phospholipids; Mediterranean diet

**Introduction**

Cancer is a major public health concern worldwide. Although cancer death rates have decreased by 26% over the last two decades (1). Despite the decline, cancer remains a major cause of mortality. At least 1 in 2 people will develop a form of cancer within their lifetime in Ireland and the UK (2, 3). Cancer is not a single disease, but a collection of related diseases that act through similar but distinctive inflammatory pathways (4). It is typically considered a disease of old age, but with increasing longevity the incidence of most cancers is increasing (5). Known risk factors fail to fully explain the patterns of cancer development. Cancers arise from the accumulation of genetic mutations, either inherited or acquired that lead to dysregulation of cell division mechanisms that induce an uncontrolled proliferation. Proliferation is accompanied by low-grade inflammation mediated by several bioactive molecules such as platelet-activating factor (PAF) that play an integral role in the tumor microenvironment, particularly in hormone-dependent cancers (6, 7).
Cells generally regulate growth through decreasing their production rate or apoptosis, but uncontrolled growth can lead to tumor development and eventually symptomatic manifestations of cancer. Generally, a healthy immune system can eradicate neoplastic cells as soon as they appear. In cancer, the immune system fails to eradicate the cancer cells and proliferative growth occurs (5). Notably lifestyle, dietary, and environmental factors account for 95% of cancers, whereas 5% account for genetic factors (8, 9). Evidently, a large proportion of cancers are preventable by diet and lifestyle modification. However, the association between nutrition and cancer is bi-directional and exceedingly complicated (5). When cancerous cells develop, nutrition may exert significant effects on the growth and involution of a tumor (5). Several studies have reported evidence of an association between individual nutrients or foods and the risk of cancer; some foods have been known to induce or protect against mutagenic effects and improve the efficiency of the immune system (5).

Inflammation is a protective physiological process of the innate immune system that occurs in response to tissue injury (10). Inflammation can be induced by both acute and chronic infections, physicochemical agents, diet, and lifestyle, which are causative and promotive of cancer (11). In some cancers, inflammatory conditions precede the development of malignancy; in others, oncogenic changes drive a tumor-promoting inflammatory milieu. Regardless of the origin of inflammation, both processes aid in the proliferation and survival of malignant cells, angiogenesis, and metastasis; subverts adaptive immunity, and alters response to hormones and chemotherapeutic agents (12). Epidemiological studies have demonstrated that systemic inflammation predisposes individuals to various types of cancer (13). It is estimated that underlying infections and inflammatory responses are linked to 15–20% of all cancer-related deaths globally (14). Cancer development due to systemic inflammation is triggered by several factors such as autoimmune diseases (e.g. inflammatory bowel disease is associated with colon cancer (15)), microbial infections (e.g. Helicobacter...
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pylori is associated with gastric mucosal lymphoma and gastric cancer (16), and inflammatory condition of unknown origin (e.g. prostatitis is associated with prostate cancer (17)). In addition, non-steroidal anti-inflammatory treatments decrease the incidence of cancers and mortality rates (18-21).

PAF is a potent proinflammatory phospholipid mediator that is implicated in the development of cancer and other inflammatory conditions such as cardiovascular disease (CVD) (22). PAF plays a major role in in angiogenesis, thrombosis, carcinogenesis, and metastasis (10, 23). However, several dietary PAF-inhibitors, particularly found in foods in the Mediterranean diet have been identified that may inhibit the physiological actions of PAF (24), thus preventing the onset of inflammatory conditions such as cancer. In this review, we explore the potential role of dietary PAF inhibitors considering the most recent literature available.

Current Status of Knowledge

PAF structure, function, signaling, and metabolism

Phospholipid mediators including prostaglandins and PAF play a significant role in several biological pathways of inflammatory diseases, including cardiovascular disease (CVD) and cancer (25, 26). The classical PAF structure (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine; Figure 1) is a prominent member of a family of molecules known as PAF-like lipids (27) that are of semi-similar or non-similar structures with similar biological activities (22, 23, 28). PAF is synthesized by various cells including neutrophils, endothelial cells, platelets, macrophages, and monocytes (10). PAF is a potent pro-inflammatory mediator that affects various cells and pathological processes (10) and is implicated in angiogenesis, thrombosis, carcinogenesis, and metastasis (10, 23). PAF and its homologous lipids 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 (PAF-R) with exceptionally high affinity (29-31). Engagement of the PAF-R by PAF or PAF-like lipids triggers an assortment of intracellular signaling cascades. This initiates biochemical mechanisms and functional responses of PAF-R bearing cells that then initiate or amplify inflammatory processes (32). The PAF-R is expressed on the surface of various mammalian cells, including leukocytes, platelets, macrophages, and endothelial cells (33, 34). PAF induced inflammatory processes are intensely involved in the initiation and progression of various cancers (22, 23, 34, 35). Although PAF-like lipids can bind to the PAF-R and initiate downstream effects, their effects are less severe than activation by PAF itself (36).

PAF can activate cells in sub-picomolar concentrations (37), thus the physiological levels of PAF are tightly regulated by the PAF metabolic enzymes. Dysregulation of PAF metabolism leads to an increase in PAF levels that exacerbates the inflammatory response. PAF is inactivated and catabolized 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 lyso-PAF (38). Lyso-PAF lacks the activity of PAF and it is cytotoxic in nature. Lyso-PAF is then reconverted into PAF or other phospholipids by the introduction of an acetyl or acyl group to the sn-2 position; hence, the biological cycle of PAF is spontaneously regulated (39). The PAF-AH enzymes are a class of enzymes that have the capacity to indirectly terminate PAF-induced signaling pathways by directly reducing either enzymatic or oxidative upregulation of increased PAF levels (23). Thus administration of recombinant PAF-AH has exhibited beneficial effects by downregulating PAF concentrations (33, 40, 41).

The primary role of PAF in physiology is to mediate cellular function and cell-cell interactions, which are critical in both physiologic and pathologic processes (42). The role of PAF is best-characterized by its involvement in the mediation of normal inflammatory responses and the regulation, blood circulation, blood pressure and regulation of coagulation...
responses (22, 42). However, it also exerts signaling functions in glycogen degradation, reproduction, fetal implantation, exocrine gland function, lung maturation, initiation of parturition, and brain function (22). PAF is synthesized by many cells on demand in response to specific stimuli, including cytokines, endotoxins, Ca^{2+} ionophores, and PAF itself (25). The biosynthesis of PAF is accomplished by two distinctive enzymatic processes; the *de novo* and the remodeling pathways (43–45). The first biosynthetic pathway is the remodeling pathway, whereby phospholipase A_2 (PLA_2) converts the ether analogues of phosphatidylcholine to lyso-PAF, which is then acetylated to PAF by isoforms of acetyl-CoA and lyso-PAF acetyltransferases (Lyso-PAF ATs, EC 2.3.1.67), notably LPCAT1 and LPCAT2 (46, 47). Evidence suggests that the production of PAF by LPCAT2 is activated under inflammatory conditions, whereas the role of LPCAT1 is still under investigation, since it is calcium independent and does not seem to engage in inflammatory processes (47).

The second PAF biosynthetic pathway is the *de novo* pathway, which initiates with the acylation of 1-0-alkyl-sn-glycero-3 phosphate by the 1-0-alkyl-sn-glycero-3 phosphate acetyl-CoA acyltransferase, followed by the sequential actions of a phosphohydrolase and the specific activity of dithiothreitol-insensitive CDP-choline: 1-alkyl-2-acetyl-sn-glycerol cholinephosphotransferase (PAF-CPT, EC 2.7.8.2), which incorporates CDP-choline into 1-0-alkyl-2-acetyl-glycerol to form PAF (44). PAF-CPT and lyso-PAF-AT both catalyze the final steps in each biosynthetic pathway and exhibit a basic regulatory role in PAF production. It is hypothesized that the *de novo* pathway is responsible for endogenous PAF production to maintain physiological levels, whereas the remodeling route leads to the production of PAF in response to inflammatory stimuli and is the main pathway involved in inflammatory cascades (23, 48). A simplified schematic of the remodeling pathway is presented in Figure 2. Long-term induction of PAF-CPT gradually increases systemic PAF levels with related consequences. Furthermore, PAF-CPT activity contributes to systemic inflammation and age-
related malfunctions of the central nervous system and cancer (23, 49), while its inhibition has demonstrated beneficial outcomes in several chronic disorders (22, 50-52).

**PAF and cancer**

- **Angiogenesis and PAF**

  The mechanism of angiogenesis, neoangiogenesis, and carcinogenesis is complex and not completely understood, in which PAF plays a significant role (34). Established tumors can increase in diameter by 1-2 mm, before their growth is inhibited by an insufficient nutrient and oxygen supply, therefore the tumor can remain dormant for several years due to the balance between proliferation and apoptosis. In this state, tumors are capable of further intrusion into proximal tissues where they can form neoplastic blood vessels driven by the hypoxic microenvironment. This process precedes metastasis and is known as neoangiogenesis, which is a promising target for cancer treatment (19-21, 53).

  Angiogenesis initiates through the activation of endothelial cells on pre-existing blood vessels by cancer cells. Chronic inflammatory manifestations facilitate endothelial activation and may induce cancer cells to secrete angiogenic factors such as PAF (23). These cancer cells produce growth factors and cytokines that link to their reciprocal receptors in the endothelium, which trigger membrane signaling pathways that stimulate the vessel. These cytokines can induce further production of PAF and expression of the PAF-R, which induces the production of more cytokines in a cyclic manner (23, 34). The activated endothelial cells also degrade the extracellular matrix (ECM) through the production of metalloproteases and serine proteases. The endothelial cells express adhesion molecules that create a microenvironment that enhances the migration and proliferation of endothelial cells from pre-existing vessels through microtubules that join the circulatory system. These newly established microtubules create a
functional tumor microenvironment that can continue to proliferate \((53, 54)\). Adhesion molecules also cause cancer cells to attach to platelets and endothelial cells in newly synthesized blood vessels, which enables metastasis and subsequent colonization of other tissues \((23, 54)\).

Angiogenic factors including cytokines, growth factors, and their specific receptors are implicated in the induction of tumor neoangiogenesis \((55-57)\). However, targeting of single growth factors or their corresponding receptors has not been successful due to the ability of cancer cells to reprogram and produce other growth factors. For example, when targeting vascular endothelial growth factor (VEGF), tumors adapt by producing basic fibroblast growth factor (bFGF) instead of VEGF, which induces the proliferation and migration of endothelial cells \((58)\). Therefore, bi-specific anti-angiogenic inhibitors have been developed that have the ability to inhibit more than one receptor, such as SU-6668 \((58)\) or Sunitinib \((59)\).

However, endothelium activation and the cascades induced by growth factors share common pathways, which are related to the production and release of lipid mediators like PAF and arachidonate \((58)\). When PAF is released in the tumor microenvironment it can affect the endothelial cells in an autocrine or paracrine mode, which can also affect platelets and cancer cells \((23)\). Increased levels of circulating PAF initiates a rapid inflammatory response that results in an increased permeability of the endothelium and other significant biological responses \((23)\), such as: 1) the increased expression of PAF-R and production of PAF by endothelial cells, platelets, and cancer cells; 2) the induction of cellular proliferation; 3) prostaglandin production via COX-2 activation; 4) expression of metalloproteases and serine proteases through the activation of the Janus tyrosine kinases (JAKs) signaling cascades and signal transducers and activators of transcription (STATs), leading to ECM degradation. These effects are crucial to the process of angiogenesis and metastasis, which are further discussed in the next section.
Several studies have indicated that PAF may be produced and PAF-R may be expressed on cell membranes of activated endothelium and/or cancer cells in the tumor microenvironment (22, 34, 49, 60-62). Cytokines and growth factors such as VEGF, FGF, and TNF-α induce PAF production (54, 63). PAF produced by these cytokines further stimulates the production of inflammatory cytokines, which promotes metastasis through activation of the NF-κB pathway via toll-like receptors (64-66). The NF-κB pathway controls the expression of pro-inflammatory cytokines (TNF-α, FGF, IL-1, IL-2, and IL-6), chemokines (IL-8, MIP-1α, and MCP-1), adhesion molecules (ICAM, VCAM, and E-selectin), acute-phase proteins, immune receptors, growth factors, and inducible enzymes (VEGF, COX-2, MMPs, iNOS), which are all implicated in inflammation, angiogenesis, or in tumor cell or endothelial cell proliferation, adhesion, migration, and invasion (67). It has been reported that PAF induces NF-κB activation in intestinal epithelial cells by enhancing IκBα phosphorylation (68). Furthermore, reactive oxygen species (ROS) activate CK2 via p38, which in turn induces NF-κB activation. Subsequently, PAF, LPS, and TNF-α increase pulmonary tumor metastasis through the induction of ROS/p38/CK2/NF-κB pathway (66). The interactions and relationships between many of these inflammatory molecules and their effects in relation to PAF and cancer are presented in Figure 3.

PAF overexpression correlates with malignancy of various tumors (34, 54). Elevated levels of PAF and PAF-R transcripts 1 and 2 are evident in hepatocellular carcinoma specimens in comparison to non-carcinoma specimens (69). In breast cancer, cells that express higher ability to synthesize and release PAF are more malignant with a higher capability to metastasize, which also express more PAF-R on their membranes (54). PAF may be involved
in breast cancer initiation as well as promotion by enhancing the migratory ability of cancer cells mediated via PI3-kinase and/or the Jun N-terminal kinase (JNK) pathway and is independent of the MAPK pathway (26). PAF also induces the transformation of non-tumorigenic cells (26). PAF overexpression in pancreatic cancer leads to cell proliferation and tumorigenesis. It has also been shown that PAF ectopic activation of the phospholipid-regulating MAPK signaling pathway via the activation of LAM TOR3 pathway, caused neoplasia in pancreatic cancer. Thus, PAF may be a biomarker for targeted therapy in pancreatic cancer (70).

PAF seems to be heavily implicated in digestive cancers. Levels of PAF-AH and PLA$_2$ are elevated in patients with colon cancer (71) and elevated PAF levels have been observed in metastatic colon cancer (72, 73). Likewise, PAF-R is strongly expressed in esophageal squamous cell carcinoma, PAF-R levels are positively correlated with malignancy in esophageal squamous cell carcinoma (74), and lysophosphatidylcholine acyltransferase 1 overexpression promotes oral squamous cell carcinoma progression via enhanced biosynthesis of PAF (75). Interestingly, PAF-R expression is also increased in patients with gastric adenocarcinoma, which is associated with organ metastasis. However, increased PAF-R expression was also significantly associated with higher tumor differentiation, smaller tumor size, absence of lymph nodes, and low tumor histopathological stage in adenocarcinoma patients who had significantly longer survival times compared to those with low PAF-R expression (76). These occurrences seem contradictory considering that increased PAF-R expression is correlated with malignancy in esophageal squamous cell carcinoma but smaller tumor size in gastric adenocarcinoma. However, the morphological features such as smaller tumor size etc. that correlate with high PAF-R expression are characteristic features of gastric cancer. These features are the reason that gastric cancer is considered slow and progressive (77), thus leading to longer patient survival (78); however, it is important to note that gastric...
cancer is still malignant and the third leading cause of cancer-related death worldwide (77). It may also be the case that the high expression of PAF-R is also a characteristic of gastric cancer, since high expression of the PAF-R may induce apoptosis (79), thus explaining why gastric cancers are slow to develop and grow, but are still lethal as they can metastasize to other organs (77). Therefore, the expression of the PAF-R in gastric cancer may have some prognostic value, but the role of PAF and the PAF-R in digestive cancers is complex and further extensive research is necessary.

PAF is present in human meningiomas where it is believed to act on tumor growth by altering the local angiogenic and/or cytokine networks as previously seen in human breast cancer and colorectal cancer (80). A recent study has indicated that PAF can alter the permeability of the blood-brain barrier (81), this may prove important for central nervous system inflammatory disorders, including cancer. PAF and PAF-R may also play a major role in prostate cancer (82).

Ultraviolet (UV) radiation is the primary cause of non-melanoma skin cancer and UV exposure is implicated in the induction of melanoma, the most severe form of skin cancer. As well as being carcinogenic, UV light is immunosuppressive (83). PAF and PAF-like lipids are produced by epidermal keratinocytes in response to UVB radiation (84, 85) and are linked to systemic immune suppression (35, 86), which is a major risk factor for skin cancer development (87). Although PAF-like lipids are produced and involved in the inflammatory milieu, they possess only 10% the potency of native PAF (36). Dermal mast cell migration from the skin to the draining lymph nodes plays a crucial role in activating immune suppression. PAF produced by UV-induced keratinocytes upregulates the expression of CXCR4 on the surface of mast cells (88). In addition, PAF upregulates CXCR4 ligand expression on lymph node cells, therefore directing the mast cell migration from the skin to the draining lymph node, where mast cells secrete IL-10 and suppress the immune response (89).
PAF synthesis by keratinocytes in response to UVB radiation is enhanced by the overexpression of the PAF-R and is inhibited by PAF-R antagonists such as WEB 2086 (90). Additionally, in B16F10 murine melanoma PAF-R antagonists decreased lung metastasis (91). Therefore, inhibition of the actions of PAF by the action of PAR-R antagonists may be a therapeutic target for the prevention of some cancers.

It was previously reported that PAF may not play a role in some human lung cancers (92). However, murine models have revealed that PAF-R antagonists can augment tumor growth and lung cancer metastasis in a PAF-R-dependent manner (93). Although PAF is critical in some cancers, it seems there is not conclusive evidence to suggest that PAF is implicated in all cancers, such as thyroid cancer (94). However, there is limited research regarding the role of PAF in various other cancers. Evidence for the role of PAF in various cancers is presented in Table 1.

Notably, PAF may exhibit beneficial effects on some cancer cells. For example, it was shown that the loss of the PAF-R in mice augmented PMA-induced inflammation and chemical induced carcinogenesis, indicating that the PAF-R may suppress PMA-induced inflammation and neoplastic development in response to chemically-induced carcinogenesis (95). Furthermore, elevated expression of the PAF-R can enhance cell apoptosis through the activation of NF-κB (79, 96), which is due to the dual action of the NF-κB pathway in malignancy and apoptosis through the immune response (97), which has been extensively reviewed by Tsoupras et al (23).

Several conclusions can be drawn from the relationship between PAF, PAF-R, and cancer. It is unknown how PAF becomes present in the tumor environment initially. It is proposed that activated endothelial cells, leukocytes, and/or platelets may synthesize PAF, which can activate other cells to produce more PAF in a autocrine, paracrine or juxtacrine way (23).
themselves synthesize PAF, which may induce neighboring cells to synthesize PAF in a similar fashion (23). Therefore, as cancer cells have the autonomy to produce PAF and express PAF-R on their membrane, PAF plays an integral role in cancer malignancy (34). While PAF is not the only mediator of inflammation involved in the complex inflammatory mechanisms of cancer, it is one yet to be fully explored or elucidated and deserves further attention for the development of therapeutic measures.

- **Types of PAF Inhibitors and Cancer**

Several molecules, both of synthetic (98) and natural (10) origins, have been described that demonstrate inhibitory effects against PAF-induced biological activities. These molecules act directly through antagonistic/competitive displacement of PAF in the PAF-R or through other indirect mechanisms. These indirect mechanisms have not yet been fully elucidated, however it is proposed that changes in the lipid rafts and membrane microenvironment of the PAF-R and/or the antioxidant capacity of these molecules may be responsible (10, 23). In addition, some PAF inhibitors such as dietary polar lipids demonstrate beneficial effects against PAF metabolism by downregulating PAF synthesis and upregulating PAF catabolism (22, 99, 100).

Many studies have focused on synthetic PAF inhibitors that modulate PAF metabolism (52) such as Rupatadine, which is used in the treatment inflammatory conditions like allergies (101-103) or cisplatin for cancer treatment (104). In addition, natural PAF-R antagonists have been described; the most well-known being ginkgolides A and B (105). Ginkgolides are a family of molecules derived from *Ginkgo biloba* tree (105), which can also modulate PAF metabolism in chronic diseases (50). In cancer, ginkgolide B has exhibited beneficial effects through inhibiting tumorigenesis and angiogenesis in azoxymethane/dextran sulfate sodium induced colitis-associated cancer in mice (106), in which tumor number and load was reduced, while
serum PAF-AH activity and thus PAF catabolism was increased and VEGF expression and microvessel density decreased following treatment with Ginkgolide B. The effects of various PAF-R antagonists including BN-50730 and WEB-2170, which exhibit anti-cancer effects through their anti-PAF activities (23, 52, 107, 108) as reviewed by Tsoupras et al. (23).

- Conventional Cancer Treatment and PAF-Receptor Antagonists

Traditional cancer treatment involves chemotherapy and radiation treatments. To date there are no PAF or PAF-R related cancer treatments available. Many in vitro and in vivo studies indicate that the co-treatment with PAF-R antagonists and chemotherapeutic drugs may have better antineoplastic effects. It has been shown that PAF-R-dependent pathways are activated during experimental tumor growth, altering the tumor microenvironment and cause the polarization of macrophages, which favors tumor growth; combination therapy of a PAF-R antagonist (WEB2170) and a chemotherapeutic drug (dacarbazine, DTIC) reduced tumor volume in mice, and the survival of tumor-bearing animals improved when both treatments were used in combination in a murine model of melanoma (109). Another study treated a SKmel37 human melanoma cell line with cisplatin, which led to increased expression of PAF-R and its accumulation. In the presence of exogenous PAF, melanoma cells were significantly more resistant to cisplatin-induced cell death. However, the use of a PAF-R antagonist WEB2086 demonstrated inhibition of PAF-R-dependent signaling pathways and exhibited chemosensitization of melanoma cells in vitro. In the same study, nude mice, that were inoculated with SKmel37 cells and treated with cisplatin and WEB2086 showed significant decreases in tumor growth compared to mice with only one treatment agent and controls. These results suggest that activation of the PAF-R pathways may support tumor survival and tumor repopulation in melanomas (110). Similarly, an in vivo study demonstrated that cisplatin
induced an increase of PAF-R expression in SKOV-3 and CAOV-3 human ovarian cancer cell lines. The upregulation of PAF-R by cisplatin correlated with a time-dependent accumulation of HIF-1α and NF-κB in the nucleus. The inhibition of PAF-R by Ginkgolide B sensitized the ovarian cells to cisplatin treatment due to the blockade of the ERK and PI3K pathways downstream of activated PAF-R. Furthermore combined treatment of ovarian cancer cells of Ginkgolide B and cisplatin reduced tumor growth (111). PAF-R antagonists may also treat intestinal mucositis as demonstrated in murine models, which is a common side effect of cancer chemotherapy (112).

Radiotherapy is important for the treatment of many cancers. Ionizing radiation is used to selectively kill tumor cells and spare normal tissue. Ionizing radiation causes significant damage to a wide variety of targets in tumor cells but it mainly causes disruption to DNA and/or DNA replication or repair mechanisms, which play a major role in radiation-induced cell death (113). However, ionizing radiation can also cause the generation of ROS (114). Pro-oxidative stressors can suppress host immunity due to their ability to generate oxidized lipids and PAF-R agonists. Sahu et al. have shown that radiation exposure of multiple tumor cell lines in vitro and in vivo, along with human subjects undergoing radiation therapy for skin tumors, all generate PAF-R agonists, which can induce several pro-inflammatory signaling pathways. Their structural analysis has revealed that radiation therapy leads to the non-enzymatic production of multiple oxidized glycerophosphocholines that are PAF-R agonists and PAF itself (115). In a murine melanoma tumor model, irradiation of one tumor led to alterations in non-treated tumors in a PAF-R-dependent process that could be blocked by cyclooxygenase-2 inhibitor. Therefore, the occurrence of PAF-R agonists as a by-product of radiation therapy could result in treatment failure. Similar results were observed in a recent study that demonstrated that PAF-like molecules with agonistic properties are generated by radiotherapy and through their action on tumor cells protects them from radiation-induced cell death by
acting on macrophages. Such PAF-like molecules stimulate tumor growth through immunosuppression. Therefore, the association of radiotherapy with the PAF-R antagonists represents a promising strategy for improving the efficacy of radiotherapy (116).

In a series of experiments by da Silva-Junior et al. (117), cervical cancer patients who underwent radiotherapy had a significantly higher expression of PAF-R. In addition, cervical cancer-derived cell lines (C33, SiHa, and HeLa) and squamous carcinoma cell lines (SCC90 and SCC78) express higher levels of PAF-R mRNA and protein than immortalized keratinocytes. Gamma radiation also increased PAF-R expression and induced PAF-R ligands and prostaglandin E2 in these tumor cells. The inhibition of PAF-R activities with the antagonist CV3938 before irradiation inhibited prostaglandin E2 and increased tumor cell death. Similarly, human carcinoma cells transfected with PAF-R were more resistant to radiation compared to those lacking the receptor. Prostaglandin E2 production by irradiated cells transfected with PAF-R were also inhibited by CV3988. These results show that irradiation of carcinoma cells generates PAF-R ligands and higher PAF-R expression that protects tumor cells from death and suggests that the combination of radiotherapy with PAF-R antagonists could be a promising strategy for cancer treatment.

Nutrition and Cancer

The links between diet and cancer have been substantiated in several epidemiological studies (118). The World Cancer Research Fund International (WCRF)/American Institute for Cancer Research (AICR) has collated and summarized published research on the relationships among cancer prevention and survivorship and diet, nutrition, and physical activity. Its Second Expert Report was published in 2007 (119) and the WCRF/AICR have since been publishing cancer prevention research from around the world. It is clear from these reports that a healthy
diet can play a key role in the prevention of cancer. In fact, they have estimated that for the 13 most common cancers, at least 29% of cases in the United States and the United Kingdom could be prevented by adhering to a healthy diet and lifestyle (120), if the research can be translated to preventive interventions, and the literature cited is valid (121).

- **Nutrition and Cancer Prevention – Inhibiting Inflammation**

Carcinogenesis is a multi-mechanism process consisting of initiation, promotion, and progression phases. Diet can affect any of these phases, but an efficacious strategy for dietary chemoprevention would be intervention during the promotion phase due to its associations with inflammation. The tumor-promotion process requires sustained exposure to agents that stimulate the growth and inhibition of apoptosis of initiated cells in the absence of anti-promoters (122).

A maladaptive diet and lifestyle are key modifiable risk factors for the prevention of systemic inflammation (123). The majority of tumor promoting conditions and agents, reversibly, inhibit cell-cell communication. However, antioxidants and anti-inflammatory agents are capable of ameliorating the effects of tumor promotors on cell–cell communication (122). Inflammatory mediators such as PAF are key molecules in cell-cell communication (10). Research demonstrates that many nutrients can modulate the immune response to act against cancerous cells, but not against adjacent cells (122, 124, 125). Certain dietary components have been proposed as possible PAF-R antagonists that may ameliorate PAF related neoplastic mechanisms (23). However, lifestyle factors are also important. For example, smoking directly affects metastatic disease via inhibition PAF-AH, resulting in the accumulation of PAF-like agonists and an increase in cell motility in breast cancer cells (126)
Many nutrients seem to possess antioxidant, anti-proliferative, and antiangiogenic properties that prevent the spread of cancer (23, 127). Several foods and supplements contain antioxidants that exhibit antineoplastic activities that function far beyond antioxidant activity alone, but also operate through direct inhibition of PAF activity and down regulation of PAF levels (23). Long chain ω3 PUFA possess multiple anti-inflammatory properties including the reduction in the synthesis of proinflammatory eicosanoids, reduction of leukocyte and platelet-adhesive endothelial interactions, inhibition of inflammatory gene expression, and stimulation of glutathione production, which can decrease oxidative injury (128, 129). Immunonutritional support in cancer treatment may modulate the immune response and improve cancer patient outcomes (129); in a double-blind study, nutritional status and inflammatory markers were improved in 40 patients with stage III non-small cell lung cancer during multimodality treatment who had taken ω3 PUFA supplements (130). Evidence suggests that ω3 PUFA supplementation may be useful in anti-cachectic therapy, and may reduce the levels of CRP and IL-6 during chemotherapy treatment of lung cancer (131). In a similar study, pancreatic cancer patients were supplemented with low doses of ω3 PUFA fish oil or marine phospholipids for six weeks. Both supplements resulted in significant weight stabilization at very low doses (300mg per day), an improved appetite, and quality of life. The phospholipid-based supplement was better tolerated than the fish oil supplement. Furthermore, both supplements increased the patient’s ω3 concentration of plasma triglycerides and phospholipids (132).

Similar outcomes were observed in patients with various tumors, who suffered tumor-associated weight loss (133). It has been concluded that ω3 PUFA supplementation during chemotherapy improves patient outcomes related to tolerability, regardless of the chemotherapy used (134). The mechanisms by which ω3 PUFA improves patient
chemotherapy tolerability are unclear (134). Positive outcomes in patients’ health may be due
to the anti-inflammatory properties of the marine phospholipids and ω3 PUFA, which have
both demonstrated anti-PAF activities and whose effects have recently been reviewed (10). The
benefits of marine PUFA supplements as an adjuvant to chemotherapy have been
comprehensively reviewed (134, 135).

Systemic inflammation is implicated in atherosclerosis (22, 123) and glomerulosclerosis
(136). Since atherosclerosis and glomerulosclerosis share common features with those of
cancer angiogenesis and metastasis, several molecules with pleiotropic activities such as anti-
atherogenic and antithrombotic molecules including warfarin, statins, vitamin D analogues,
and non-steroidal anti-inflammatory molecules such as COX-2 inhibitors have demonstrated
beneficial effects against cancer (137, 138). Several of these treatments exhibit inhibitory
effects against the bioactivities of PAF and its biosynthetic enzymes (52). Polar lipids
(phospholipids, sphingolipids, glycolipids, and phenolic lipids) that are widely distributed in
foods have the capacity to inhibit the biological actions of PAF (10). These lipids are
structurally specific and bind to the PAF-R directly or indirectly (10). Polar lipids extracts from
marine and dairy sources (10, 99, 123, 139) have demonstrated the ability to inhibit PAF-
induced platelet aggregation in animal and human platelets in cardiovascular related studies.
These studies investigate the potential of various food lipids to inhibit the binding of PAF to
the PAF-R through direct antagonistic or competitive binding. Observing the inhibition of
PAF-induced platelet aggregation by dietary polar lipids allows for the identification of PAF-
R antagonists. These studies identified phosphatidylcholine and phosphatidylethanolamine
derivatives as the biologically active polar lipids against the actions of PAF (10, 140), which
also had the ability to modulate PAF metabolism, with beneficial outcomes against
atherosclerosis (10, 51, 100, 141).
Therefore, it is logical to propose that molecules that can inhibit the binding of PAF to PAF-R and its subsequent signaling pathways, may possess the same beneficial biological activities in cancer. Certainly *in vitro* and *in vivo* studies indicate that polar lipid compounds can affect PAF metabolism (100) and have anti-proliferative effects against human ovary and colon cancer cells (142), although not all of the mechanisms are fully elucidated. In particular, phosphatidylcholine may induce apoptosis (143) and inhibit DNA synthesis in colon cancer (144). Furthermore, polar lipids and phenolic compounds in red and white wine have also demonstrated antiproliferative effects in prostate cancer cells (PC-3) (145). These effects were attributed to their antioxidant effects, as the PAF pathway was not assessed.

Dairy products are consumed in moderation in most dietary patterns. Polar lipids isolated from bovine, ovine, and caprine dairy products have exhibited potent inhibition of PAF-induced platelet aggregation *in vitro* (146-149). Interestingly, caprine and ovine milk lipids seem to possess greater anti-PAF activity in contrast to bovine milk lipids and that fermented products may exhibit greater bioactivity (150). This is attributed to the structural differences between these polar lipids.

Studies directly investigating dietary polar lipids with anti-cancer activities are limited. However, a food grade extract rich in polar lipids from the milk fat globule membrane of buttermilk were strongly antiproliferative against human ovary and colon cancer cells (OVCAR-3 and HT29) (142). Similarly, buttermilk polar lipids inhibited the growth of SW480 colon cancer cells in a dose dependent-manner. This study determined that a sphingolipid fraction mainly composed of lactosylceramide downregulated growth-signaling pathways mediated by β-catenin, ERK1/2 (extracellular signal-regulated kinase), phosphorylated Akt (serine/threonine-specific protein kinase), and c-myc (151). Extensive study of sphingomyelin and related compounds confirms that they play a central role in the control of cell growth, differentiation, migration, and apoptosis and may have therapeutic value (152, 153).
Specifically, dairy derived-sphingomyelin is reported to decrease the number of aberrant foci crypts and protect against colon cancer by inhibiting tumorigenesis and increasing alk-
sphingomyelinase in mice fed a concentration of 0.5 g/kg over 22 weeks *ad libitum* (154) and the supplementation of 0.005 g/100 g sphingomyelin in the diet of CF1 mice transformed malignant adenocarcinomas to benign adenomas (155).

Other murine models have shown that dietary supplementation of dairy-derived sphingomyelin may also be chemopreventative when administered before tumor induction (154, 156-159). These effects are attributed to ceramide and sphingosine phosphate, which induce apoptosis by modification of the expression of regulator genes in cancer (160, 161). The literature suggests that that sphingomyelin may be the most active polar lipid against cancer (156). Furthermore, these anti-cancer phospholipids seem to share similar compositions to those that demonstrated inhibition of PAF-induced platelet aggregation and thus the PAF inflammatory pathway (148). In particular, it has been confirmed that dairy-derived sphingolipids inhibit the binding of PAF the PAF-R in PAF platelet aggregation studies (146-148). Therefore, it is possible that these molecules may also inhibit PAF-related mechanisms in cancer, as was been previously postulated (23).

Polar lipids from other sources have exhibited similar effects on various cancer cell lines. For instance it has been shown that microalgae polar lipids may induce anti-proliferative effects in MCF-7 breast cancer cells (162), however a similar study of dairy polar lipids did not observe the same effects (142). This may be due to the differences in the polar lipids composition or their isolation techniques (156). The same microalgae study also demonstrated a 50% decrease in growth of hepatic cancer cells (Hep-G2) (162). In a similar *in vitro* study of hepatic cell lines (Alexander cell, Hep-3b, Hep-G2, and HuH-7), phosphatidylcholine isolated from egg yolk inhibited cancer cell growth. A study of the same cells in Sprague-Dawley rats administered the same polar lipid concentrates (0.05 g/100 g of diet) in an intragastric manner.
over 14 weeks exhibited similar inhibition of growth (163, 164). Similarly, polar lipids may be beneficial in the treatment and prevention of pancreatic cancer (165).

Phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin have displayed positive effects against metastasis in gastric cancer cells (NUGC) by decreasing migration and adhesion (166). Although not dietary, synthetic phosphatidylethanolamine has demonstrated various antiproliferative, anti-angiogenic, and anti-metastatic effects in murine renal cell carcinoma and HUVEC cells. Furthermore, *in vivo* results show that phosphatidylethanolamine potentially inhibits lung metastasis in nude mice, with a superior efficacy when compared to Sunitinib (167). Although not specified in these studies, it is likely that inhibition of the PAF pathway could play a role. Considering these findings, further research should address the possible role of dietary phospholipids for the prevention of neoangiogenesis, cell proliferation, and metastasis through the PAF pathways.

Other nutrients including phenolic-lipids like resveratrol, yuccaols, and epigallocatechin-3-gallate found in various foods also exhibit beneficial effects against the PAF inflammatory pathways (52, 108, 168). However, there is a lack of substantial mechanistic evidence to explain their observed effects.

**The Mediterranean diet and cancer**

*The traditional Mediterranean diet and cancer prevention*

Several studies have linked the Mediterranean diet to lower risk of cardiovascular disease (169). Evidence suggests that this may extend to lower incidences of other chronic diseases mediated by inflammation including diabetes (170), cerebrovascular disease (171) cancers of the digestive system (172-175), breast cancer (176), overall types of cancer (177, 178), and premature mortality in general (179). The traditional Mediterranean diet is broadly characterized by high fruit, vegetable, legume, bread, cereal foods composed of wheat, tree
nuts, and olive oil consumption, including moderate helpings of milk and dairy products, and low intake of red meat (24). Wine is also consumed within moderation in non-Islamic regions. Coffee is considered the hot beverage of choice and is generally consumed with sugar (119). The compounds and nutrients found in the Mediterranean diet seem to exhibit bioactivities against PAF-related inflammation, cancer development, and metastasis. Detopoulou et al. (180) examined the effects of nutrition, lifestyle, and biochemical variables of 106 subjects. Dietary patterns and food constituents containing bioactive molecules were inversely related to PAF levels or its biosynthetic enzymes. It is uncertain whether this association is facilitated by the attenuation of subclinical inflammation induced by an antioxidant-rich diet or is it a direct action of antioxidants on PAF metabolism. Nevertheless, this association illustrates a potential mechanism of the diet–disease hypothesis.

It has been proposed that the Mediterranean diet may in part exert some of the observed beneficial effects through dietary PAF antagonists such as polar lipids, which reduce PAF-related cascades implicated in platelet activation, aggregation, and inflammation (10, 24, 148, 181, 182) as many foods of the Mediterranean diet are rich in compounds with anti-PAF biological activities. A clinical study has demonstrated that meals high in PAF antagonists improved the platelet response of type II diabetics and healthy humans against inflammatory and prothrombotic factors (183). A similar study demonstrated that the traditional Greek Mediterranean diet can reduce platelet activity in type II diabetics and healthy volunteers due to the effects of PAF antagonists on PAF- and ADP- induced platelet aggregation (181). Although the molecular mechanisms have not been fully elucidated yet, diets that contain high levels of PAF antagonists may play a role in inhibiting the biological actions mediated by PAF, thus potentially lowering the risk of cancer. Indeed, other similar healthy dietary patterns such as the Nordic diet may also exert its beneficial effects against cancer in part via dietary PAF inhibitors and related anti-inflammatory mechanisms (184).
Furthermore, it is not clear whether the presence of other health conditions (e.g. cardiovascular diseases, obesity, etc.) in patients with cancer may compromise or improve the efficacy of dietary PAF inhibitors against PAF, and subsequently cancer; thus, further research is warranted. Some of the foods and compounds of the Mediterranean diet that exhibit these effects are summarized in Table 2.

**Cancer incidence and the Mediterranean diet**

A recent meta-analysis that included 83 studies assessed the adherence to the Mediterranean diet on the risk of overall cancer mortality and the risk of various cancers in a total of 2,130,753 subjects. It was found that the highest adherence score to a Mediterranean diet was inversely associated with a lower risk of cancer mortality, head and neck cancer, breast cancer, gastric cancer, liver cancer, colorectal cancer, and prostate cancer. However, the association between the adherence to the highest Mediterranean diet category and the risk of cancer mortality and cancer recurrence in survivors was not statistically significant. Furthermore, it was demonstrated that these protective effects were associated with high fruit, vegetable, and whole grain intake (185). Other studies have demonstrated similar results with varying levels of statistical strength for overall cancer and specific cancers (172, 175, 186-188), in particular in southern Europe, adherence to the Mediterranean diet was associated with a 6% reduction in cancer mortality (177). It is clear that adherence to the Mediterranean diet is associated with a reduction in mortality and morbidity, which is due to the types of foods consumed and the nutrients that the diet provides and they possess anti-inflammatory bioactivities (189). Hence, the presence of nutrients that have the capacity to inhibit PAF and related inflammatory pathways may in part play a significant role in inflammation and cancer. While PAF plays a central role in several key mechanisms of cancer development and
progression, and there is a plethora of inflammatory pathways interlinked in an exceedingly complex process, it is important to note that blocking one inflammatory mediator is not a panacea. Dietary PAF inhibitors may have the potential to prevent the physiological actions of PAF in cancer, but it must be acknowledged that this is only one of many mechanisms. The adherence to healthy dietary patterns rich in microconstituents with anti-inflammatory bioactivities such as those of the Mediterranean diet, may in part aid in impeding multiple pro-inflammatory mechanisms.

However, concern has been raised that the traditional Mediterranean dietary patterns are gradually becoming less common as the food supplies of the countries of the Mediterranean littoral become increasingly ‘Western’ (119). The Western diet is associated with high intake of processed food, which may lead to anywhere between 25% - 50% of total daily energy intake, which is synonymous with the U.S. (190). A recent perspective cohort study found that a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase greater than 10% in risks of overall cancer and breast cancer (191). Furthermore, there is evidence of a higher risk for colorectal cancer in Western societies where there is higher consumption of processed meat and red meat, although there are concerns that red meat itself unprocessed may not be negatively associated with colorectal cancer risk (192). This is in contrast to those who adhere to the Mediterranean diet that benefit with lower overall cancer mortality (193). A recent study has demonstrated that adherence to a Western style diet was related to an increased risk of breast cancer, especially in premenopausal women. Whereas, the Mediterranean diet was related to a lower risk. These observations were again attributed to a diet high in fruits, vegetables, and oily fish (175). Therefore, it is clear that the modern Mediterranean regions should adhere to their traditional dietary patterns, as Westernization may lead to an increase of chronic diseases including cancers.
Future Research Perspectives

PAF plays a central role in digestive, skin, breast, and reproductive cancers, but may not be involved in other cancers and has demonstrated attenuating effects in some cancers. Many studies have demonstrated that PAF-R antagonists may inhibit cancer growth and affect PAF metabolism in several cancers. Additionally, PAF antagonists may be useful as an adjuvant therapy for current chemotherapy and radiation treatments. Certainly, the PAF pathway is a novel target for developing cancer treatments and recently PAF was proposed as a biomarker of cancer. In light of these findings, several dietary PAF inhibitors such as polar lipids present in various components of the Mediterranean diet may affect cancer occurrence and development. Furthermore, the Mediterranean diet is associated with a lower incidence of various cancers. Many compounds of the Mediterranean diet exhibit anti-PAF activities, which may be partly responsible for some of these beneficial observations. However, these anti-inflammatory mechanisms have yet to be fully elucidated and further molecular studies are required to decipher the precise mechanisms that govern PAF-induced inflammation, angiogenesis, and metastasis. Although the PAF pathway may be an attractive therapeutic target for various inflammatory diseases, it is not yet certain whether this would be advantageous to inhibit PAF in human cancer. Therefore, randomized controlled trials are required to assess the use of PAF-R antagonists as an adjuvant mode of treatment in cancer.

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Nutrition, PAF, inflammation, and cancer


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Nutrition, PAF, inflammation, and cancer


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### Table 1: The role of PAF in various cancers.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Role of PAF and PAF-R</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer cells</td>
<td>Increased PAF production and PAF-R expression promotes migration, proliferation of tumor cells, and neoangiogenesis</td>
<td>(26, 54)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>PAF-AH and PLA₂ are elevated in patients. Metastatic colon cancer cells exhibit elevated levels of PAF</td>
<td>(71-73)</td>
</tr>
<tr>
<td>Esophageal squamous cell carcinoma (ESCC)</td>
<td>PAF-R is overexpressed in OSCC and correlated with malignancy. Lysophosphatidylethanolamine acyltransferase 1 overexpression promotes OSCC progression via enhanced biosynthesis of PAF</td>
<td>(74, 75)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>PAF-R expression is increased in patients with gastric adenocarcinoma and is associated with higher tumor differentiation, smaller tumor size, absence of lymph node, and organ metastasis, and low tumor histopathological stage. Patients with elevated PAF-R expression have significantly longer survival times compared to those with low PAF-R expression</td>
<td>(76)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC)</td>
<td>Elevated levels of PAF and PAF-R involved in the angiogenic response in HCC</td>
<td>(69)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>The role of PAF in lung cancer is not clear; PAF-R antagonists can augment tumor growth and lung cancer metastasis in a PAF-R-dependent manner in murine models. In a double-blind study, nutritional status and inflammatory markers were improved in 40 patients with stage III non-small cell lung cancer during multimodality treatment who had taken ω3 PUFA supplements. ω3 PUFA supplementation may possess anti-cachectic effects and reduce inflammatory markers during chemotherapy treatment of advanced inoperable non-small-cell lung cancer</td>
<td>(93, 130, 131)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>PAF overexpression in pancreatic cancer leads to cell proliferation and tumourigenesis through MAPK signaling</td>
<td>(70)</td>
</tr>
<tr>
<td>Renal cell carcinoma (RCC)</td>
<td>CD154-induced PAF production and PAF-R expression stimulate cell proliferation motility, growth, and dissemination of RCC</td>
<td>(194)</td>
</tr>
<tr>
<td>Skin Cancers - melanoma and non-melanoma</td>
<td>PAF and PAF-like lipids are produced by epidermal keratinocytes in response to UVB radiation and are linked to UVB-induced systemic immune suppression. PAF synthesis is enhanced by the overexpression of the PAF-R</td>
<td>(35, 84-86, 90)</td>
</tr>
</tbody>
</table>

1 HCC, hepatocellular carcinoma; ESCC, esophageal squamous cell carcinoma; PAF, platelet-activating factor; PAF-AH, platelet-activating factor acetylhydrolase; PAF-R, platelet-activating factor-receptor; PLA₂, phospholipase A₂; PUFA, polyunsaturated fatty acids; RCC, renal cell carcinoma
Table 2: Studies examining the anti-PAF activities of whole foods and polar lipid extracts in the Mediterranean diet.

<table>
<thead>
<tr>
<th>Studied Food and Components</th>
<th>Study Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL of fish (Cod, coley, haddock, mackerel, salmon, sardines, seabass, and seabream)</td>
<td>In vitro studies in WRP, hPRP, and HMCs</td>
<td>Inhibition of PAF-PA Modulation of PAF metabolism towards reduced PAF levels and reduction of atherosclerotic lesions in hypercholesterolaemic rabbits (51, 140, 195-200)</td>
</tr>
<tr>
<td>PL of olive oil and olive pomace</td>
<td>In vitro studies in WRP and HMCs</td>
<td>Inhibition of PAF-PA Modulation of PAF metabolism towards reduced PAF levels and reduction of atherosclerotic lesions in hypercholesterolaemic rabbits and regression of existing lesions (201, 202)</td>
</tr>
<tr>
<td>PL of dairy products</td>
<td>In vitro studies in WRP and hPRP</td>
<td>Inhibition of PAF-PA (146-148)</td>
</tr>
<tr>
<td>PL of goat and sheep meat</td>
<td>Ex vivo studies in hPRP</td>
<td>Inhibition of PAF-PA (203)</td>
</tr>
<tr>
<td>PL of seed oils (corn, sesame oil, sunflower oil)</td>
<td>In vitro studies in WRP</td>
<td>Inhibition of PAF-PA (204)</td>
</tr>
<tr>
<td>PL of hen eggs</td>
<td>In vitro studies in WRP</td>
<td>Inhibition of PAF-PA (205)</td>
</tr>
<tr>
<td>PL of red and white wine, musts, grape skins, and yeast</td>
<td>In vitro studies in WRP and U937 macrophages Postprandial dietary intervention studies in humans Ex vivo studies in hPRP</td>
<td>Inhibition of PAF-PA Modulation of PAF metabolism towards reduced PAF levels (99, 100, 206-209)</td>
</tr>
<tr>
<td>PL of honey</td>
<td>In vitro studies in WRP</td>
<td>Inhibition of PAF-PA (210)</td>
</tr>
<tr>
<td>EOE of garlic &amp; onion</td>
<td>In vitro studies in WRP</td>
<td>Inhibition of PAF-PA (211, 212)</td>
</tr>
<tr>
<td>Wild plants of the Mediterranean diet (Reichardia picroides, Cynara cardunculus, Urospermum picroides, and Chrysanthemum coronarium)</td>
<td>In vitro studies in WRP Postprandial dietary intervention studies in humans</td>
<td>Reduced postprandial platelet hyperaggregability of metabolic syndrome patients Inhibition of PAF-PA <em>ex vivo</em> Inhibition of PAF-PA <em>in vitro</em> (213)</td>
</tr>
<tr>
<td>Compounds of the Mediterranean diet found in oils, herbs, spices, tea, wine, etc. (PL, hesperidin, luteolin, naringin, oleic acid, oleuropein, proanthocyanidins, quercetin, resveratrol, tyrosol)</td>
<td>In vitro studies in WRP and hPRP</td>
<td>Inhibition of PAF-PA (214, 215) Modulation of PAF metabolism towards reduced PAF levels (168, 216, 217)</td>
</tr>
</tbody>
</table>

1 EOE, essential oil extract; HMCs, human mesangial cells; hPRP, human platelet-rich plasma; PA, platelet aggregation; PAF, platelet-activating factor; PL, polar lipids; WRP, washed rabbit platelets
List of Figure Legends:

Figure 1: The structure of platelet-activating factor.

Figure 2: The remodeling pathway of PAF and lyso-PAF biosynthesis. PAF-AH converts active PAF to the inactive lyso-PAF by the loss of an acetate group at the sn-2 position. Lyso-PAF AT converts lyso-PAF back to the active PAF by the reincorporation of an acetate back to the sn-2 position. Acetyl-CoA, acetyl coenzyme A; AT, acetyltransferase; Lyso-PAF, lyso-platelet-activating factor; PAF, platelet-activating factor; PAF-AH, platelet-activating factor acetylhydrolase.

Figure 3: A schematic of the key biological events surrounding PAF-induced inflammation in the tumor microenvironment, angiogenesis, and metastasis. These biological events are inextricably linked and exacerbate in inflammatory conditions. aFGF, acidic fibroblast growth factor; bFGF, basic fibroblast growth factor; COX-2, cyclooxygenase-2; HGF, hepatocyte growth factor; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor 1; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein; MMPs, matrix metalloproteinases; PAF, platelet-activating factor; PAF-R, platelet-activating factor-receptor; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; RNS, reactive nitrogen species; VCAM, vascular adhesion molecule; VEGF, vascular endothelial growth factor.
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