Review Article
Targeting the key factors of inflammation in cancer: plant intervention

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Abstract: The association between inflammation and cancer has earned significant recognition and acceptance. The activation of genes controlling inflammation cell signaling pathways can lead to the controlling of all aspects of the disease process. Of these pathways, NF-κB, STAT-3, HIF-1, TNF-α, IL-1, Cox-2 and oncogenic Kinase (IKK, MARK/ERK, Syk/Src, IRAK1/4, JAK, and P13k) play a fundamental role in connecting inflammation and cancer. For this reason, cancer-related inflammation serves as a target for innovative prophylactic and therapeutic intervention. Recently, novel therapeutic concepts aim at interrupting the activity or expression of inflammatory mediators implicated in cancer initiation and promotion, either in single-agent or combinatorial treatment or as supplements of the current therapeutic approach. Phytochemicals and nutraceuticals have achieved noteworthy acknowledgment in the prospective management of various human clinical conditions. Research has demonstrated that plant extracts have proven to be less toxic and very effective chemoprophylactic and therapeutic agents since they possess the ability to suppress specific molecular and cellular pathway in cancer-related inflammation. Therefore, targeting the inflammatory signaling pathways offers the chances to boost the clinical outcome of cancer therapy. Here we provide a new insight into recent advances on the links between inflammation, as they relate to cancer. Also, we reviewed recent findings on plant extracts and phytochemicals that have been scientifically evidenced to exert chemopreventive and chemotherapeutic effect via the inhibition of the key inflammatory events involved in cancer initiation and progression. Our findings highlight the opportunities for future research and further investigation of the identified plants and phytochemical for anti-cancer drug discovery.

Keywords: Cancer, inflammatory mediators, phytochemicals, plant extracts, chemopreventive, chemotherapeutic, drug discovery

Introduction

Cancer remains one of the world's deadliest diseases, and according to the American Cancer Society, In the United States, there will be an estimate of 1,688,780 new cancer cases diagnosed and 600,920 cancer deaths in 2017 [1]. The World Health Organization reported a global estimate of 14.1 million new cancer cases and 8.2 million cancer-related deaths in 2012 [2]. Regardless of tremendous progress in treatment over the past decade, neither the prevalence of the illness nor the deaths due to cancer have positively changed within recent years. Researchers are considering different therapeutic approaches in the quest to eradicate cancer, and this has led to the discovery of many theories. Amongst these theories includes the association of inflammatory markers with cancer cells. Since the nineteenth century when Rudolf Virchow established the link between inflammation and cancer, an avalanche of epidemiological, experimental and clinical studies has been conducted to confirm cancer-related inflammation [3-5]. Also, approaches to testing a lot of synthetic anti-inflammatory molecules in cancer research have yielded promising preclinical results. However, unexpected adverse effects or insufficient anticancer activity when tested in humans has hampered their translation to clinical practice. A good number of anti-cancer drugs that modulate only single targets have emerged over the past decade; however, cancer is a disease caused by disturbance of several signaling pathways. Therefore, targeting
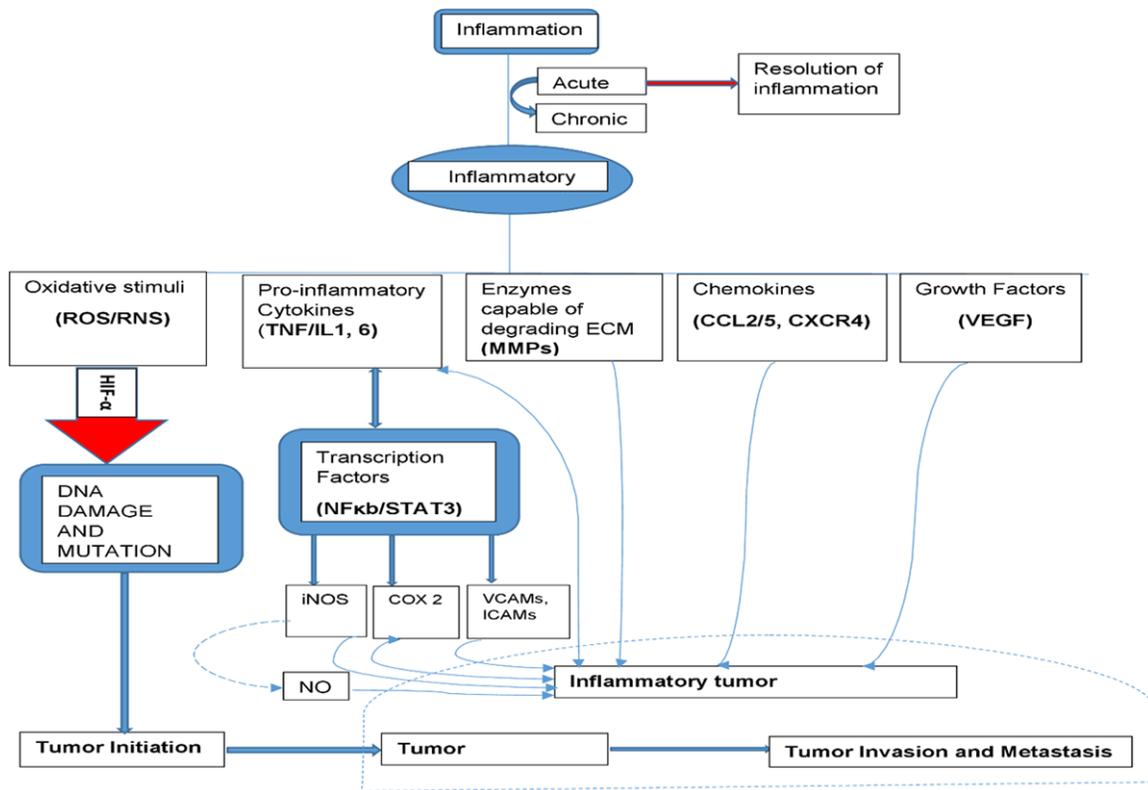
Figure 1. Pathways that connect inflammation and cancer.
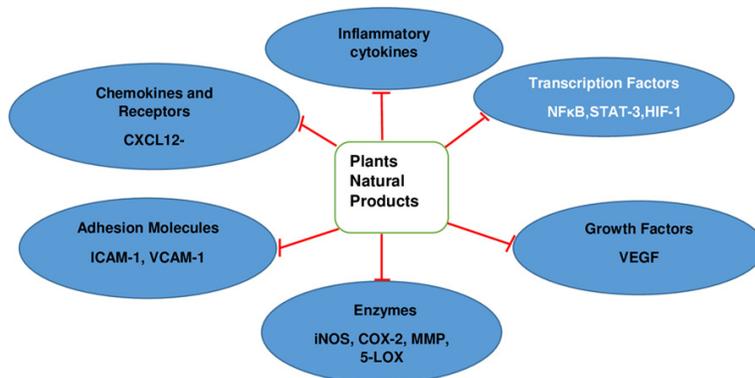
Figure 2. Molecular Targets Modulated by Plant Natural Products.

tic tool has been increasing considerably. Abundance studies have established a strong link between consumption of certain fruits, vegetables, and certain spices to the reduction of cancer risk. A vast variety of phytochemicals found in foods and medicinal plants endowed with high anti-inflammatory activities have demonstrated preventive or protective effects against the tumor in different organs of experimental animals and arrest the growth of neoplastic cells [6-15]. These naturally occurring anti-inflammatory agents' acts as either preventing agents, which inhibit the tumor initiation step through stopping carcinogen activation. Also as suppressing agents, which inhibit tumor mobile proliferation for the duration of the promotion and metastasis stages of tumorigenesis by inducing or suppressing specific cellular anti-inflammatory activities and the related molecular signaling pathways [16]. These findings have displayed that phyto-

only one of these multiple pathways in cancer management makes it almost impossible to achieve disease control. Additionally, these single-target drugs cause a lot of adverse events and are often very costly. These limitations of available anti-cancer drugs underscore the significance of identification of pharmacological agents that can modulate multiple targets, innocuous, inexpensive, and handy for the prevention and treatment of cancers. The use of herbal-derived natural products as a therapeu-

chemicals possess the potential to obstruct the molecular events in the cancer initiation, promotion, and progression stages. The evidence that more than 39 completed or ongoing clinical trials in the USA focused on phytochemicals and nutraceuticals (clinicaltrials.gov: accessed on 14th March 2017) supports the vital role they play in the prevention and treatment of cancer. Herein, we intended to summarize recent developments and hypotheses on research published on the cancer chemopreventive and chemotherapeutic effects of plant products, and focusing on mediators of the key factors of inflammation in cancer.

Inflammation and cancer: overview

The increased body of evidence from epidemiological, preclinical and clinical studies demonstrates that dysregulated inflammatory response plays a significant role in various chronic ailments including cancer. Inflammation is an important protective response that can eliminate primary triggers (foreign organisms, dead cells or physical irritants), and also contribute immensely to the initiation of tissue regeneration of injured tissues by mediating an organized immune response. When this happens, there is coordinated blood-borne delivery to damaged tissues of cells, and soluble mediators involve in both innate and adaptive immunity. After tissue disruption following inflammation, macrophages and mast cells secrete matrix remodeling proteins, cytokines, and chemokines, activate local stromal cells (e.g., fibroblasts, adipocytes, vascular cells) to recruit circulating leukocytes into damaged tissue (acute inflammation), to eliminate pathogens [17-19]. Brief or acute inflammation is a self-limiting process and has a possible therapeutic outcome, whereas the imperfect or incomplete resolution of inflammatory responses owing to dysregulation in immune response can lead to persistence of lymphocytes and leukocytes (granulomas) in the cellular microenvironment, leading to various phases of tumorigenesis [20, 21]. Moreover, chronic inflammation of tumor microenvironment has been evidenced to trigger cellular events, which promotes and aggravates the malignant development of cancer cells [22]. The molecular mechanism(s) by which chronic inflammation promotes tumor cell proliferation, transformation, invasion, metastasis, angiogenesis, chemoresistance, and radioresistance is via upregulated expression of pro-inflammatory mediators such as reactive oxygen species (ROS), factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducer and activator of transcription-3 (STAT3), etc (**Figure 1**). The release of (ROS) and reactive nitrogen species can damage DNA at the site of the tumor [23]. The free radicals and aldehydes produced results in a modification of cancer-associated genes and posttranslational alteration in the primary cell signaling proteins involved in cell cycle, DNA repair and apoptosis [24]. Furthermore, ROS is known to activate various transcription factors such as activator protein 1 (AP-1), Hypoxia-inducible factor 1-alpha (HIF-1a), NF-κB, STAT3, resulting in the expression of proteins that regulates inflammation [25]. NF-κB and STAT3 transcription factor are the main links between inflammation and tumorigenesis and can be critical to promoting preneoplastic as well as malignant cells escape from apoptosis [26-28]. Many cancers activate NF-κB. Hence it is regarded as a significant inflammation mediator, and an oncogenic key transcription factor [29]. In fact, increased levels of NF-κB can lead to the hostile nature of many tumor events [26, 27, 29, 30]. A great body of evidence have confirmed the negative contribution of the chronic inflammatory process to various phases of tumorigenesis, such as cellular proliferation, transformation, apoptosis evasion, survival, invasion, angiogenesis and metastasis [31, 32]. Also, from epidemiological studies, chronic inflammation has been implicated as a predisposing factor for the pathological progression of various types of cancers and there exist several parallel relationships between inflammation and host response to malignant disease [33, 34]. Studies have shown that underlying infections and inflammatory responses account for up to 15-30% of all death from cancer worldwide [35]. Accumulating evidence suggests the strong link between prolonged inflammatory processes and cancer; such as inflammatory bowel disease (IBD) association with high risk of colorectal cancers [36, 37], chronic hepatitis B virus (HBV) infection caused liver cirrhosis and hepatocellular carcinoma (HCC) [38, 39], reflux esophagitis caused Barrett's esophagus and esophageal adenocarcinoma [40], the link between ovarian cancer and ovarian epithelial inflammation [41-43], Chronic Infections associated Chronic Inflammation and Squamous Cell Carcinoma [44]. Moreover, emerging studies have established the significant persistent

role; unresolved inflammation plays in the promotion and progression of breast cancer [45, 46]. Also, some studies have provided unequivocal evidence that there is a close link between the immune system constituents to cancer progression and chronic inflammation. For instance, chronic inflammation is linked with immunosuppression mediated primarily by immature myeloid-derived suppressor cells (MDSCs). Many factors influence MDSC differentiation arrest leading to suppression of the host's innate and adaptive immune systems which was supposed to contribute immensely to antitumor responses [47, 48]. Therefore, there is growing evidence that supports the link between chronic inflammation and cancer development.

Targeting the key factors of inflammation in cancer

Targeting the oncogenic kinases

Several studies have shown the functional activation of critical protein kinases, consisting of the IkB kinase (IKK) and mitogen-activated protein kinases (MAPKs) like p38 MAPK, c-Jun NH2-terminal kinase (JNK1/2), and extracellular signal-regulated kinase 1/2 (ERK1/2) in tumorigenesis. Also, there are proven evidence of the involvement of oncogenic kinase in activating inflammatory transcription factors (such as NF-kB and AP-1) and other pro-inflammatory mediators (such as Inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α)) associated with carcinogenesis [49]. Another oncogenic kinase which is immensely involved in the inflammatory process is the protein kinase B (Akt). In an experimental model of Akt-knockout mice and cells of liver cancer, it was established that the inhibition of Akt was directly proportional to the inhibition of NF-kB. Suggesting that Akt can activate the IKK. IKK, in turn, induces the phosphorylation of IkBα (inhibitor of kappa B) leading to the translocation and activation of NF-kB and the activation of NF-kB results to the activation of pro-inflammatory mediators [50]. The inhibition of these chains of actions via the modulation of any of this kinase may proffer a good solution in cancer treatment. The inhibition of Akt, phosphatidylinositol 3-kinases (PI3K), and Janus Kinase (JAK; which transduce cytokine-mediated signals via the Jak-STAT

pathway) collectively exerted anti-inflammatory activity, as demonstrated in lipopolysaccharide (LPS)-stimulated BV-2 microglial cells [51]. The experiment also showed a decrease in the production of proinflammatory cytokines and chemokines [51]. Similarly, in acute kidney injury, the suppression of ERK and PI3K/Akt pathways attenuated inflammation process [52]. Suggesting that PI3K, Akt, and JAK may be involved in modulation of inflammatory responses, cytokines, and chemokines. Besides, in LPS-Activated BV-2 Microglial Cells, the suppression of Akt/NF-κB and MAPKs/AP-1 pathways remarkably decreased inflammatory events [53]. Indeed, these kinases are involved in the elicitation of pro-inflammatory cytokines, as demonstrated in experimental multiple sclerosis where the downregulation of PI3K/Akt, JNK and p38 MAPK and subsequent inhibition of pro-inflammatory cytokines were observed upon treatment with cannabidiol (Cannabinoids, the secondary metabolites found in the plant *Cannabis sativa*) [54]. The suppression of Spleen tyrosine kinase (Syk)/Src and Interleukin-1 receptor-associated kinase 1 (IRAK)1/4 markedly resulted in the suppression of (NF)-kB and activator protein (AP)-1. Which consequently attenuated inflammation [55]. Furthermore, a liberal estimate of the Inflammatory myofibroblastic tumor (IMT) have been established to have a rearrangement of anaplastic lymphoma kinase (ALK) gene [56], as it was again recently reported in a clinical case of intraosseous IMT of the mandible [57]. Although, however, to the best of our knowledge, there have not been any publication on plant products that inhibits ALK. Thus, a call for more investigations.

Targeting transcription factors

Accumulating evidence over the past decades presents NF-κB and STAT3 pathways as key molecular links between chronic inflammation and carcinogenesis. These transcription factors regulate inflammatory reaction and stimulate tumorigenesis through production/recruitment of soluble mediators like cytokines (e.g. IL-6), chemokines (e.g. CCL2) and other cellular components (e.g. Tumor-associated macrophages (TAMs)) [58, 59]. Although some studies have reported the anti-inflammatory role of the activation of NF-κB [60-62], however, in this context, anti-inflammatory intervention by way of inhibiting the NF-κB signaling pathways has

proven to be potential for prevention and treatment of inflammatory-associated cancers [63-65]. NF-κB and STAT3 are often constitutively activated in various human cancer cells leading to the expression of transcription factor regulating genes and subsequent proliferation, invasion, angiogenesis, and ultimately the survival of cancer cells [66]. NF-κB is seen as an important orchestrator of innate immunity and inflammation and has exhibited the capability of regulating the activities of both, preneoplastic and malignant cells. In both situations, NFκB is found downstream of the perceiving of a microorganism or tissue damage through the toll-like receptor (TLR)-MyD88 pathway, the inflammatory cytokines TNFα and IL-1β. Upon activation by the degradation of its inhibitor IkBa, NF-κB is translocated to the nucleus, where it induces the upregulation of several genes that can result in cell-autonomous genetic alterations, suppression of apoptosis, proliferation, invasion, metastasis, chemoresistance, radio-resistance and inflammation in cancer cells. Several of the activated target genes for inflammatory cytokines, adhesion molecules, and key inflammatory enzymes are essential for the progression to various stages of aggressive types of cancer. Substantial genetic data, involving precise targeting of gene components of the Ikk complex, like IkappaB-kinase beta (IKKβ), have unraveled enough clues on the role of NF-κB in tumor pro motion [67]. In vitro and in vivo studies have cited that constitutive activation of NF-κB results in inhibition of chemotherapy-induced apoptosis in some cancer cells. Furthermore, a link between innate immunity to the response to hypoxia can be due to interconnections and compensatory pathways between NF-κB and Hypoxia-inducible transcription factor-1 (HIF1α) [68]. Earlier reports show that NF-κB regulates the transcription of HIF-1α, whereby the activa tion of NF-κB led to increased HIF-1_ mRNA levels in tissues exposed to hypoxia [69]. HIF-1α is known to mediate adaptive response to hy poxia, current clinical and in vitro studies have reported the involvement of hypoxia in tumor progression [70] and drug resistance in lung cancer cells [71]. Furthermore, NF-κB has again presented itself as a convenient molecular target for cancer therapy by also controlling the activities of MMPs. Ming et al. suggested that the nuclear export of NF-kappaB-p65 consequently reduced the expression of metalloproteinases (MMP)2 and MMP9, which led to met-

astatic inhibition induced by a ginseng saponin, compound K (CK) [72]. Tumor-associated immune cells, as well as inflammatory cells, can activate STAT3 signaling, which makes STAT3 an important intrinsic pathway for cancer inflammation. Also, malignant cells can activate an enormous number of genes (such as IL-6, IL-10, IL-11, IL-17, IL- 23, CXCL12, and COX-2) that are essential for inflammation [73]. STAT3 has shown the ability to control several intracellular signal transduction pathways of various pro-inflammatory cytokines, chemokines and other mediators like macrophage colony-stimulating factor, prostaglandins and cyclooxygenase-2 (COX-2) which have demonstrated to stimulate and maintain a cancer-promoting inflammatory environment [74-76]. Furthermore, the persistent activation of STAT3 can not only stimulate cellular proliferation through controlling genes linked with cell cycle progression but also aid tumor angiogenesis, resistance to apoptosis [77, 78] and immunosuppression [79]. Therefore, both NF-κB and STAT3 can serve as attractive molecular targets for treating and preventing chronic inflammation-induced cancers.

Targeting of inflammatory chemokines and their receptors

Chemokines are members of small (8-14 kDa) groups of proteins that interact with receptors on cell surfaces during physiological processes in the body, directing cells to particular sites in the body. Recently, they have been identified to modulate many intracellular signaling pathways, including NF-κB, STAT families, and MAPKS. Various cell types, like endothelial cells, fibroblasts, epithelial cells, tumor cells, stromal cells and tumor-associated leukocytes have been identified to have the ability to produce chemokines [80-82]. They remain to be powerful attractants of leucocytes, like neutrophils, monocytes, natural killer cells and T cells. They are structurally classified into four subgroups of CXC, CC, CX3C and C; and are functionally categorized as inflammatory, homeostatic or both [83]. Chemokines promote carcinogenesis by either regulating tumor transformation, survival, growth, invasion or metastasis or by promoting angiogenesis and tumor-leukocyte interactions. Murakami, et al. demonstrated that a CXCR3- and CXCR3/CXCR4 double-knockdowns significantly decreased the dissemination of cancer cells to liver and lungs [84]. Detectable

levels of CXCR7 have been found on the surface of murine breast tumor 4T1 and Lewis lung carcinoma (LLC) cell lines [85], which are known to form primary and metastatic tumors in mice [86]. The CXC chemokines having the ELR motif are the classical inflammatory and angiogenic chemokines [87]. ELR+ CXC chemokines like CXCL8 (1L-8) can promote tumor growth by enhancing angiogenesis and the chemoattraction of neutrophilic granulocytes. Neutrophils in turns promote angiogenesis, tumor growth, and metastasis via inducing matrix-degrading enzymes and angiogenic tumor-promoting factors like vascular endothelial growth factor (VEGF) [88, 89]. Contrarily, ELR- CXC chemokines like CXCL10, have angiostatic abilities. It binds to CXCR3 attracting anti-tumoral lymphocytes. However, CXCL12 as an ELR- chemokine is the angiogenic exception, because it moderates angiogenesis through its normal receptor CXCR4 [81]. The production of CXCL12 in bone marrow, CNS, lungs, liver and lymph nodes has been proven to cause the activation of CXCR4, which in turn controls tumor cell migration [90]. Melanoma cells may exhibit CCR10 that recognizes CCL27 and CCL28 hugely expressed by skin epithelium [91]. Breast cancer tumor cells show distinct chemokine receptors, CXCR4 and CCR7, being some of them. In an orthotopic mouse model, obstruction of the CXCL12-CXCR4 axis inhibited metastasis of the cell line MDA-MB-231 to the lung [92]. Many studies have discovered noticeable blockage of metastasis using both CXCR4 antagonists and CXCL12-specific blocking antibodies in different tumor cell lines [93]. The chemokine CXCL8 (IL-8) and its receptors CXCR1/2 have demonstrated to be potential therapeutic targets in various solid tumors like malignant melanoma, colon, breast, and bladder cancer [94].

Targeting inflammatory cytokines

Cytokines such as TNF-α and IL-1 and IL-6 act by modulating NFκB and STAT families of transcription factors [95-97], which are known for their proto-oncogenic abilities and their prolonged abnormal activation are directly involved in the pathogenesis of different forms of tumors. The activation of such likely oncogenic transcription factors by cytokines and other components of the tumor may connect inflammatory environment, cancer, and immune cells and directly promote tumor initiation and progression by enhancing the survival factors and

through modulating the tumor microenvironment. Therefore, cytokines have been recognized as key component and orchestrator of the inflammatory microenvironment of tumors. Hence, cytokines and cancer seem "inseparable". The release of cytokines by cancer cells have led to the recruitment of endothelial cells, fibroblasts, and infiltrating inflammatory cells to the site [98, 99]. Moreover, the recruitment of satellite cells to the tumor sites due to excessive secretion of cytokines forms a complex regulatory network that controls the activities of the tumor microenvironment [99]. TNF-α as pro-inflammatory cytokine is one of the most studied cytokines and has shown to mediate the initiation, promotion, and metastasis of tumors [100-102]. In the tumor environment, TNF-α causes the activation of NF-κB, leading to expression of inflammatory genes including reactive oxygen intermediates, inflammatory cytokines and chemokines, inducible cellular adhesion molecules, cyclooxygenase, and MMPs [59]. A recent study showed that TNF-α induced the activation of tumor necrosis factor-α-induced protein 8 (TNFAIP8), which contributes to tumor aggressiveness and poor prognosis in patients with invasive ductal breast carcinoma [103]. Specimens from archival tissue from patients with advanced stages of colorectal cancer show Significantly higher levels of TNF-α mRNA [104]. Furthermore, TNF-α can activate NF-κB in cell types possessing TNF receptors [105, 106], suggesting that the inhibition of TNF-α usually, leads to suppression of NF-κB. Moreover, certain phytochemicals which suppress TNF-α and also exhibit inhibitory activity against NF-κB activation [107, 108].

IL-1β is a pleiotropic cytokine exhibiting many roles in both physiological as well as pathological conditions. It is known to be up-regulated in different tumor types and can promote tumor progression through the upregulation of metastatic and angiogenic genes and growth factors [109]. The virulent phenotype exhibited by some tumors has been ascribing to high IL-1β concentrations within the tumor microenvironment [110]. Many tumors, like gastric, breast, neck, colon cancers and others were reported to overexpress IL-1β [111-113]. IL-1 can stimulate the upregulation of metastatic genes as well as proinflammatory genes like VEGF, IL-6, IL-8, TGFβ and MMPs [111]. Recent research on chemoresistance revealed that drug-resistant human hepatocellular cancer (HCC) cells de-

rived IL-6 activated MDSCs both in C57BL/6N mice and in HCC. The experiment showed that the blockade of IL-6 signaling was directly proportional to the depletion of MDSCs, which in turn correlates with the chemotherapy response in patients [114]. Another clinical research also demonstrated that IL-6 promotes the nuclear translocation of Protein arginine methyltransferase-5 (PRMT5) expression that lead to poor clinical outcome in oropharyngeal squamous cell carcinoma (OPSCC) patients [115]. Inhibition of IL-6 using an anti-IL-6 receptor antibody obstructed the development of colitis-associated colorectal cancer (CAC) and reduced expression of HIF-1α, suggesting that IL-6 promotes CAC progression by regulating HIF-1α expression during the early stages of CAC development [116]. In contrast with other cytokines, IL-10 is the primary inhibitory cytokine produced by T(T$_{Reg}$) cells that suppress the expression of many pro-inflammatory cytokines and chemokines, as well as proinflammatory enzymes [117]. Perhaps the induction of IL-10 can be a useful anti-inflammatory mechanism as seen in experiments where the increased production of IL-10 stimulated by the administration of maqui and calafate extract showed an inhibitory effect on inflammatory response [118]. Besides, in non-small-cell lung cancer patients treated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), a decrease in IL-10 plasma levels corresponded with the severity of rash [119]. Although, there exist some other publications that suggest the inhibition of IL-10 for lung cancer therapy [120, 121]. Even So, based on our finds in the present review, we do not recommend the inhibition of IL-10 for cancer therapy, indicating the need for more research to clarify the implications of IL-10 in lung cancer. Taken together, these cytokines have proven to be directly or indirectly (by modulating other molecules) involved in various types of cancers, making them a promising target for cancer therapy. Finally, these cytokines have proven to be directly or indirectly (by modulating other molecules) involved in various types of cancers, making them a promising target for cancer therapy.

Targeting inflammatory enzymes

Several enzymes such as Cyclooxygenase-2 (COX-2) and iNOS can modulate the progression from inflammation to cancer. COX (cyclo-oxygenase) pathway which is one of the signaling pathways involved in tumorigenesis, exist as two main COX isoforms, COX-1 and COX-2, that shows different expressional characteristics between tissues. COX-2 which is known as the rate-limiting isoform takes care of prostanoid production during inflammation and their overexpression can lead to many cancers. Several studies have demonstrated the upregulation of COX-2 in multiple forms of cancers, such as carcinomas of the urinary bladder, colon, breast, prostate, and lung [122-125]. Furthermore, increased expressional levels of PGE2, an enzymatic product of COX-2, has been found in many tumors like colorectal, lung, breast, pancreatic, and hepatocellular carcinoma [126-129]. Transformation of arachidonic acid to prostaglandins due to activities of COX-2 has shown to be mitogenic, resulting in cellular proliferation [130]. Moreover, COX-2 is a promising molecular target for natural compounds in cancer chemoprevention and therapy [131] and its capability to stimulate angiogenesis and direct malignant phenotype, has been recognized as a potential initial diagnostic marker of the virus linked human malignant neoplasms [132]. iNOS an inflammation-driven enzyme that catalyzes the production of nitric oxide (NO), overexpresses in various malignancies as well as many inflammatory processes [133]. Several clinical studies from humans and laboratory animals have demonstrated the connection between iNOS and the development of many tumors. Increased iNOS expression has been detected in breast cancer [134, 135] and various other cancers like lung [136], Bladder [137], Human Melanoma [138], and Skin [139].

Targeting adhesion molecules

Adhesion molecules are extensively expressed on the cell surface, basement membrane and extracellular matrix (ECM). They promote cell-cell as well as cell-matrix interactions which are vital for different physiological and pathological mechanisms of blood coagulation, cell growth, differentiation and trafficking, embryogenesis, immune responses, inflammation, wound repair and tumor development. Recent studies have demonstrated that, besides their role in adhesion, these molecules can also work as signal transducers to modulate numerous cellular activities via G-proteins, phospholipids and protein kinases [140]. A growing body of

Table 1. A list of plant extracts and the inflammatory events they inhibit

#	Plant source	Part used	Model description	Possible molecular targets	References
1	*Lavandula dentata*	Aerial parts	NBS model of rat colitis and carrageenan-in- duced paw edema in mice	MMP-9, iNOS, COX-2, IL-1β, IL-6 and TNFα	[262]
2	*Lavandula stoechas*	Aerial parts	NBS model of rat colitis and carrageenan-in- duced paw edema in mice	MMP-9, iNOS, COX-2, IL-1β, IL-6 and TNFα	[262]
3	*Pistacia vera*	Hulls	Lipopolysaccharide-stimulated RAW 264.7 macrophage cells	NO, ROS COX-2 and IL-6	[263]
4	*Schisandra chinensis*	Fruits	Human SW1353 chondrosarcoma cells	MMPs, IL-1β, COX-2, iNOS and NF-κb.	[264]
5	*Amaranthus Lividus*	Leaves	Ages-induced cells	TNF-α, IL-1 and IL-6	[265]
6	*Amaranthus tricolor*	Leaves	Ages-induced cells	TNF-α, IL-1 and IL-6	[265]
7	*Uncaria sinensis*	Hooks and stems	Murine BV2 Microglia stimulated with LPS and photothrombotic cortical ischemia-induced brain injury	NO, PGE2, TNF-α, IL-1β, IL-6, COX-2 and NF-kb	[266]
8	*Iberis amara*	Whole plant	Adjuvant-induced arthritis model of inflammation.	TNF-α, PGE2, and IL-1β	[267]
9	*Jasminum lanceolarium*	Stems and roots	Carrageenan-induced rat paw edema model	PGs, COX-2 and 5-LOX	[268]
10	*Lonicera caerulea L.*	Fruits	Human leukemia monocytic THP-1 Cell line derived macrophages stimu- lated by LSP	PGE2, TNF-α, IL-6 and COX-2	[269]
11	Black Rice	Whole grain	LSP-stimulated RAW 264.7 macrophage cell line	NO, iNOS, MAPK, ERK, TNF-α, IL-6, COX-2, AP-1 and NF-kb.	[49]
12	*Lonicera japonica*	Flower buds	Lipopolysaccharide (LPS)-stimulated BV-2 microglial cells	NO, iNOS, PGE2, MMP-9, MAPKs, ERK 1/2, JNK, PI3K, Akt, TNF-a and IL-1b, STAT 1/3 and NF-kb.	[51]
13	*Quercus sideroxyla*	Leaves	HT-29 cells	COX-2, IL-8 and NF-κb	[270]
14	*Medicago sativa*	Stem	LPS-stimulated RAW 264.7 mouse macrophage cells	IL-1β, IL-6, and COX-2	[271]
15	*Trianthema portulacastrum*	Aerial parts	Chemically Induced Rat Mammary Tumorigenesis	COX-2 and NF-κb, IκB Nrf2	[272]
16	*Acanthopanax senticosus*	Roots	Mouse model of lipopolysaccharide-induced acute lung injury	TNF-α, IL-6, and NF-kb	[273]
17	*Hippophae rhamnoides*	Leaves	LPS induced endotoxemia in Balb/c mice	iNOS, COX-2, IL-6 and TNF-α	[274]
18	*Psacalium decompositum*	Roots	Obesity fructose-induced in Wistar rats	IL-6, IL-1β, IFN-γ, MCP-1 and VEGF	[275]
19	*Thymus serpyllum*	Aerial parts	Trinitrobenzene sulfonic acid (TNBS)-induced rat colitis and dextran sodium Sulfate (DSS)-induced mouse colitis	iNOS, ICAM-1, COX-2, TNF-a, and IL-6 IL-1β, MCP-1, and IFNγ	[276]
20	*Polygala sabulosa*	Aerial parts	LPS-induced peritonitis in mice	TNF-α, IL-1β and IL-6	[277]
21	*Retama monosperma*	Aerial parts	Intra-colonic administration of Trinitrobenzene sulfonic acid (TNBS) in rats (a Crohn's disease model)	iNOS, COX-2, NF-kB, IκB, and p38MAPK	[278]

Table 2. A list of isolated compounds illustrating the inflammatory events they inhibit

#	Compound	Plant source	Chemical class	Model description	Possible molecular Targets	References
1	4-hydroxy-acetophenone	*Salsola tuberculati- formis*	Phenolic	Streptozotocin model of type 1 diabetes	IL-1β, TNF-α and IL-6	[279]
2	Senecionine	Senecio brasiliensis	Alkaloid	Mouse model of pleurisy induced by carrageenan.	TNF-α, NF-κb and IL-1β.	[108]
3	Integerrimine	Senecio brasiliensis	Alkaloid	Mouse model of pleurisy induced by carrageenan.	TNF-α, NF-κb and IL-1β.	[108]
4	Senecionine N-oxide	Senecio brasiliensis	Alkaloid	Mouse model of pleurisy induced by carrageenan.	TNF-α, NF-κb and IL-1β.	[108]
5	Isorhamnetin-glucosyl-rhamnoside	*Opuntia ficus-indica*	Flavonoid	Croton oil-induced ear edema model.	NO, COX-2, TNF-α, and IL-6	[280]
6	Pinosylvin	*Pinus sylvestris*	Stilbene	Carrageenan-induced paw inflammation stilbenes in the mouse	NO, iNOS, IL-6, and MCP-1	[281]

7	Monomethylpinosylvin	*Pinus sylvestris*	Stilbene	Carrageenan-induced paw inflammation in the mouse	NO, iNOS, IL-6, and MCP-1	[281]
8	Delphinidin 3-sambubioside	*Hibiscus sabdariffa*	Flavonoid	RAW264.7 cell model and LPS-Induced Paw Edema in Mice	iNOS, NO, MCP-1, IL-6, and TNF-a, NF-кb, and MEK1/2- ERK1/2	[282]
9	Hispidulin	*Clerodendrum inerme*	Flavone	RAW 264.7 murine macrophage cell model	NO, iNOS, PGE_2, JNK, COX-2 and NF-кb	[283]
10	Quercetin	*Eucommia ulmoides*	Flavonoid	Hepatocellular carcinoma (HCC) cell model	NF-кb	[284]
11	Catechin-(5,6-bc)-4α, β-(3,4-dihydroxyphenyl)-dihydro-2(3h)-pyranone	*Eucommia ulmoides*	Flavonoid	Hepatocellular carcinoma (HCC) cell model	NF-кb	[284]
12	Eucommioside-I	*Eucommia ulmoides*	Iridoid	Hepatocellular carcinoma (HCC) cell model	NF-кb	[284]
13	Icariside F2	*Eucommia ulmoides*	Flavonoid	Hepatocellular carcinoma (HCC) cell model	NF-кb	[284]
14	Gentiolactone	*Gentiana triflora*	Secoiridoid dilactone	Murine Macrophage model	iNOS , TNF-α, and Cox-2	[285]
15	2,8-dihydroxy-7H-furo[2,3-f]chromen-7-one	*Tibouchina paratropica*	Phenolic Derivative	Human-derived monocyte THP-1 cells (ATCC 202).	IL-6	[286]
16	Schisantherin A	*Schisandra sphenanthera*	Dibenzocyclooctadiene	LPS-induced mouse ARDS	IкB-α, ERK JNK, MAPKs, TNF-α, IL-1β , IL-6 and NF-KB	[159]
17	Dauca-8, 11-diene-7-one	*Boesenbergia longiflora*	Sesquiterpenes	Murine macrophage RAW264.7 cells	NO, iNOS and COX-2	[287]
18	Kaempferol-3,7,40-trimethylether	*Boesenbergia longiflora*	Flavonoid	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
19	Kaempferol-7,40-dimethyl ether	*Boesenbergia longiflora*	Flavonoid	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
20	Rhamnazin	*Boesenbergia longiflora*	Flavonoid	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
21	Pinostrobin	*Boesenbergia longiflora*	Flavonoid	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
22	Dihydrobisdemethoxycur-cumin	*Boesenbergia longiflora*	Diarylheptanoids	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
23	1-hydroxy-dihydrobisdemethoxycurcumin	*Boesenbergia longiflora*	Diarylheptanoids	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
24	Dihydro-bisdemethoxycurcumin-40, 4"-diacetate	*Boesenbergia longiflora*	Diarylheptanoids	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
25	Demethoxycurcumin	*Boesenbergia longiflora*	Diarylheptanoids	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
26	Bisdemethoxycurcumin	*Boesenbergia longiflora*	Diarylheptanoids	Murine macrophage RAW264.7 cells	NO and TNF-α	[287]
27	Mansoins B	*Mansoa hirsuta*	Flavonoid	LPS-stimulated THP-1 cells	TNF-α	[288]
28	8-epiloganin	*Castilleja rubra*	Iridoid	LPS stimulated RAW264.7 macrophages	NO, TNF-α, IL-1β, NF-кb and PGE_2	[289]
29	Mussaenoside	*Castilleja rubra*	Iridoid	LPS stimulated RAW264.7 macrophages	NO, TNF-α, IL-1β, NF-кb and PGE_2	[289]
30	5-O-caffeoylshikimic acid	*Castilleja rubra*		LPS stimulated RAW264.7 macrophages	NO, TNF-α, IL-1β, NF-кb and PGE_2	[289]
31	Cycloeucalenone	*Solanum cernuum*		Carrageenan-induced paw edema Model	COX-2	[290]
32	24-oxo-31-norcycloartanone	*Solanum cernuum*		Carrageenan-induced paw edema Model	COX-2	[290]
33	Bergenin	genus *Bergenia*	Tannins	Mouse Model Of LPS-Induced Mastitis	NO, NF-кB, TNF-α, IL-1β, IL-6 and MAPK	[291]

evidence suggests that modifications in the adhesion abilities of neoplastic cells play a crucial role in tumorigenesis and the biological nature of many malignancies [141]. Several cell adhesion molecules (CAMs) including large CAM superfamilies like the immunoglobulin (Ig)-like CAMs, cadherins, selectins, and integrins are involved in the pathogenesis of different types of tumors. The immunoglobulin (Ig)-like CAMs includes molecules that participate in cellular immunity (MHC antigens, CD2, CD4, CD8 and the T cell receptor) and leukocyte trafficking. Also, neural cell adhesion molecule, vascular addressin, epithelium-specific adhesion molecules, carcinoembryonic antigen, MAdCAM-1, MUC18 and deleted in colorectal carcinoma (DCC) [142]. Ding, Yong-Bin, et al. have demonstrated that expression of VCAM-1 is closely related to oncogenesis, tumor angiogenesis and metastasis in gastric carcinoma [143]. Clinical investigations have indicated that enforced expression of ICAM-1 may be embroiled in the pathogenesis and prognosis of a vast number of tumors including breast and hepatocellular cancer [144, 145]. Indeed, the de novo release of ICAM-1 on gastric cancer cells corresponds with a heightened prospect of hematogenous metastasis by suppressing local anticancer immunity [146]. NF-kB p105 (p50 precursor), knockout mice, show decreased ICAM-1 expression [147], suggesting that NF-kB can induce ICAM-1 and VCAM-1. Also, STAT transcription factor is an important activator of ICAM-1 expression [148, 149]. Moreover, Pro inflammatory cytokines, such as IL-1β and tumor necrosis factor α (TNF-α), stimulates cancer cell adhesion, resulting to cancer metastases by promoting the expression of adhesion molecules such as ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) [150, 151].

Therapeutic intervention by plant

Numerous plant extracts have been used in traditional folk medicine as an effective remedy for different types of illnesses. Moreover, such traditional medicine is widely used in practiced to date. Since the practice of traditional medicine is not strictly based on evidence gathered using the scientific method, modern medicine recognizes it as a form of alternative medicine. Nonetheless, modern medicine make use of many plant-derived compounds as the basis for evidence-tested pharmaceutical drugs, phyto-

therapy, and phytochemistry. Currently, modern standards are being employed to test the efficacy of herbs and medicines that are derived from natural sources. However, the constituents of these natural product extracts represent a vast unexploited source of potentially novel biologically active molecules. In this review, we identified recently isolated compounds from various plants (**Figure 7** and **Table 2**), that are proposed anti-inflammatory phytochemicals for cancer therapy. Furthermore, **Table 1** contains a list of plant extracts with potential inhibitory properties to the key factors of cancer-related inflammation and may provide a new source of chemicals for the effective treatment of cancer. Our findings showed that not much reports had been published about bioactive proteins from plant sources; particularly on inflammation, indicating the need for more research because plant proteins like Lectins have been reported to have multiple biological activities, including immunostimulation, repression, and antitumor activity [152]. Also, in A549 cells experiment, Agglutinin a lectin isolated from *Arisaema heterophyllum* Blume suppressed PI3K/Akt signaling pathways and consequently induced apoptosis and autophagy in A549 cells [153].

Plant extract mixture is a known traditional medical practice that involves the combination of two or more plant extracts Herbal mixtures. Herbal mixtures have proven to be an excellent medical remedy for various diseases. It is believed that the synergy between different constituents of the plants enables them to be more efficiently active. Japanese pharmaceutical companies manufactured formulations known as Kampo formulations, which constitute of mixtures of crude extracts from the bark, leaves, roots, or rhizomes of different herbs. These formulations and several other formulations are recognized by the Japanese national health insurance system and controlled by government regulations [154, 155]. Recently, the Japanese herbal medicine known as Daiokanzoto (TJ-84), a Kampo formulation composing of crude extracts of Rhubarb rhizomes and Glycyrrhiza roots have been reported to reduce the production of IL-6 and CXCL8 by lipopolysaccharide-stimulated oral epithelial cells and gingival fibroblasts [156]. Green tea polyphenol, epigallocatechin-3-gallate and cranberry proanthocyanidins act in synergy with cathelicidin (LL-37) to reduce the secretion of

Figure 3. Chemical structure of phenolic compounds.
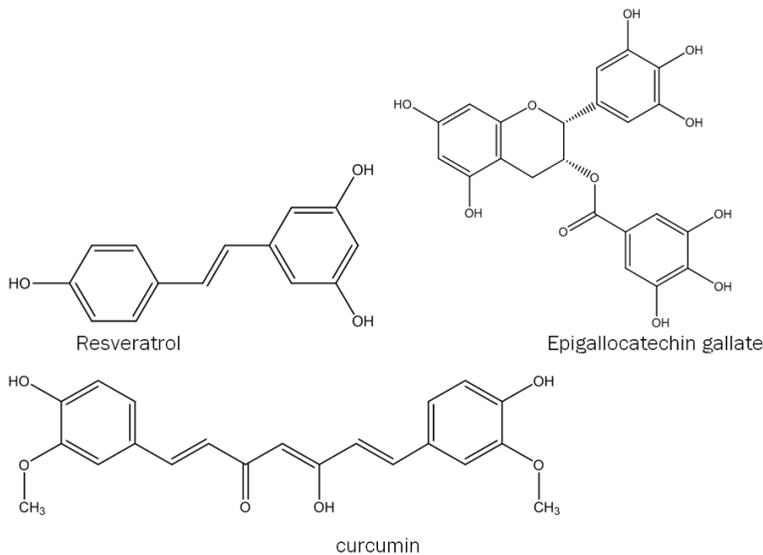
tumorigenic, anti-inflammatory, and antioxidant agent [160]. Several studies have reported that resveratrol interferes with many of the key players mediating inflammation, blocking DNA damage and inducing apoptosis in a p53-dependent manner [161, 162]. The generation of two key metabolites namely piceatannol and 3,4,5,4'-tetrahydroxy stilbene through hydroxylation of resveratrol by CYP1B1 have been reported [163-166], and these metabolites notably enhance its chemopreventive actions by inhibiting tyrosine kinase and activating apoptosis. The chemopreventive and chemotherapeutic pleiotropic properties of resveratrol have been extensively investigated in both in-vitro and in vivo studies in different forms of cancers including breast, prostate, lung, skin, and colon [167-169]. Experimental data have proven that resveratrol may conquer chemo-resistance in most cancer cells by way of inhibiting NF-Kb and STAT3 pathway [170, 171]. These observations had also been supported through an inhibition of NF-κB and STAT-3 in patients with multiple myeloma [172]. Resveratrol has been found to inhibit the PI3K and Akt pathway in acute lymphoblastic leukemia cells [173]. Additionally, it has extensively brought about the degradation of HIF-1a protein by using the proteasome pathway. Recently a novel resveratrol analog, HS-1793, has been confirmed to inhibit vascular endothelial growth factor (VEGF) and HIF-1α in human prostate cancer cells [174]. Resveratrol has shown a whole lot promise in preclinical trials, and due to its desirable safety profile, it could be a significant chemopreventive and chemotherapeutic agent. However, the fast metabolism of resveratrol has been a continuing setback.

IL-6 and IL-8 in LPS-induced inflammatory response in a three-dimensional co-culture model of gingival epithelial cells and fibroblasts [120]. Another potent herbal mixture is the Chinese propolis. Chinese propolis has been acknowledged for its wide range of biological properties and pharmacological activities [157, 158]. In a study involving the combination of Chinese propolis and buds from poplar (*Populus canadensis*), it was observed that this combination suppressed the secretion of LPS-stimulated inflammatory cytokines, such asinterleukin-6 (IL-6) and TNF-α production in endotoxemic mice [159]. Given the illustrated effectiveness of these herbal mixtures, it signifies that a combination of different plant extracts that have been individually identified to modulate the inflammatory mediators could be a novel adjunctive therapy for the treatment of cancer.

Effects of selected phytochemicals

Phenolics

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a phenolic (**Figure 3**) phytoalexin which exists in several plant species, generally seen as a constituent in red wine, skins or bark of grapes, pistachios, blueberries, and peanuts. Phytoalexins, are presumed to be synthesized by plants following injury or stress, for instance, if an infectious microorganism contaminates the plant. They produce valuable impact as an anti-

Curcumin is a polyphenol which is a component of the golden spice turmeric (Curcuma longa). Over the past decades, extensive studies have given more insights into the medicinal and health advantages of curcumin. Many publications have reported its anti-inflammatory [175], chemopreventive, and anti-carcinogenic [176-178] properties. Curcumin can interfere with

several extracellular and intracellular molecules which are actively involved in cancer proliferation, differentiation, invasion, apoptosis, and cell cycle checkpoints, thereby inhibiting the progression of most cancers [12, 179-181]. Increasing evidence suggests that the inhibitory outcomes of curcumin on tumor cells are due to their modulatory effect on the growth of tumor cells through regulation of multiple cell signaling pathways. These pathways comprise caspase activation (caspase-8, 3, 9), cell proliferation (cyclin D1, c-Myc), cell survival (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), tumor suppressor (p53, p21) death receptor (DR4, DR5), mitochondrial, and protein kinase (JNK, Akt, and AMPK) pathways [182]. Mishra, Alok, et al. reported that curcumin can selectively suppress transcription of the HPV16/E6 oncogene via inhibition of the activity of host nuclear transcription factors AP-1 and NF-kB in oral cancer cells [183]. Also, curcumin suppressed LPS-induced EMT through downregulation of NF-κB-Snail signaling in breast cancer cell [184]. Curcumin can abolish NF-κB pathway in multiple cancer cells [181], colorectal cancer [185, 186], pancreatic cancer [187], head and neck squamous cell carcinoma [188], adenoid cystic carcinoma [189], oesophagal adenocarcinoma [190], human biliary cancer [191], medulloblastoma [192], gastric cancer [193], Myeloid-derived suppressor cells [194], ovarian cancer [195] and prostate cancer [196]. Curcumin significantly inhibited rat colorectal carcinogenesis via peroxisome proliferator activated receptor-γ (PPAR-γ) [197]. Yang, et al. demonstrated that curcumin can suppress small cell lung cancer (SCLC) cell proliferation, cell cycle, migration, invasion, and angiogenesis via inhibiting STAT3 [198]. The constitutive phosphorylation of STAT3 seen in ovarian and endometrial cancer cells have been inhibited by curcumin [199]. Curcumin was shown to suppress the expression of TNF-α in Hepatocellular Carcinoma [200]. Curcumin prevented colon carcinogenesis by suppressing lipopolysaccharide (LPS)-induced expression of iNOS and COX-2 [201]. A study found that curcumin reduced metastasis to the lung and abrogated the expression of NF-κB, MMP-9, COX-2, VEGF, and ICAM-1 in a human breast cancer [202]. Hence, because of its efficacy as well as modulatory effects of multiple targets, couple up with its safety for human consumption, curcumin has received considerable attention as a possible therapeutic agent for the prevention and treatment of different malignant diseases.

Epigallocatechin gallate (EGCG), a flavanol also known as epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid and is a type of catechin. It is the most available catechin in tea. Epigallocatechin gallate has been shown in some studies to inhibit tumor cell growth and may have beneficiary effect against metastasis. In SHRSP.Z-Leprfa/IzmDmcr (SHRSP-ZF) obese and hypertensive rats, EGCG inhibited the development of hepatic premalignant lesions by improving liver fibrosis, suppressing RAS activation, and attenuating inflammation and oxidative stress. The quantitative realtime RT-PCR analysis revealed that, in the livers of SHRSP-ZF rats, EGCG significantly decreased the expression levels of MMP-2, MMP-9, and TGF-b1. Moreover, the hepatic expression levels of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1b were significantly decreased. Suggesting that EGCG might also be able to prevent non-alcoholic steatohepatitis (NASH)-related liver fibrosis tumorigenesis [203]. This inhibitory effect of EGCG on the inflammatory mediators (IL-6, IL-1b, and TNF-α,) is in concordance with the suggestion that Chronic inflammation is one of the pathophysiological mechanisms involved in the development of hepatocellular carcinoma (HCC) in NASH [204]. Again, pre-administration of EGCG significantly blunted the expression of IL-β1, IL-6, and TNF-α, in lungs treated with fluoride [205]. EGCG can be potential chemopreventive agents against cholangiocarcinoma, as it decreased the elevated phosphorylated-STAT1 and STAT3 proteins, suppressed the cytokine-induced expression of inducible nitric oxide synthase (iNOS) and intercellular adhesion molecule-1 (ICAM-1), which are the key molecules involved in inflammatory and tumorigenic processes [206]. Furthermore, in a drug-induced tissue injury model, EGCG attenuated cisplatin-induced TNFα and IL1β mRNA and decreased the amount of NF-κB (p65) [207].

Organosulfur compounds

Organosulfur compounds are a group of chemical compounds (**Figure 4**) which contains both carbon and sulfur, for example, Sulforaphane (SFN). SFN falls within the isothiocyanate group of organosulfur compounds which are present in cruciferous vegetables such as broccoli,
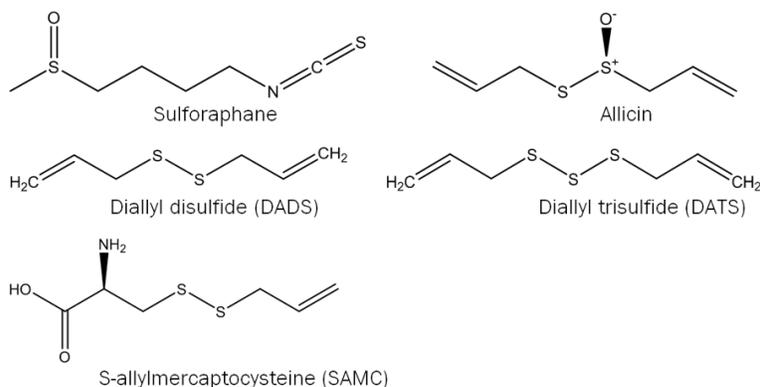
**Figure 4.** Chemical structure of organosulfur compounds.

SFN via the nucleotide-binding oligomerization domain containing protein 2 (NOD2) pathway [217]. Furthermore, Arif *et al.* investigated the effect of SFN on human breast cancer cells. They found that the administration of SFN was able to inhibit the expression level of COX-2, suppressed the growth of breast cancer cells and also boosted the therapeutic index of the chemotherapeutic drug, Gemcitabine [218].

Brussels sprouts or cabbages. SFN is produced as a result of damage to the plant (such as from chewing) which permits a reaction involving the transformation of glucoraphanin, a glucosinolate precursor, into sulforaphane by the plant enzyme myrosinase. The consumption of Cruciferous vegetables has been evidenced to reduce lung cancer risk [208]. SFN is considered a potential chemopreventive and chemotherapeutic agent due to its ability to target multiple inflammatory events involved in the pathogenesis of cancer. In prostate cancer orthotopic model, the consumption of SFN suppressed NF-κB and other NF-κB associated target molecules such as IL-6 and IL-8, HIF-1α, and COX-2 were significantly reduced [209]. These activities of SFN eventually resulted in an improvement in the therapeutic potentials of tumor necrosis factor related apoptosis inducing ligand (TRAIL) [209]. SFN has consistently inhibited the gene expressions of pro-inflammatory and pro-carcinogenic signaling factors such as NF-κB, TNF-a, IL-1b, IL-6, IFN-b, IL-1b, COX-2, iNOS, CCR4, and CXCR4. As shown in many publications [210-213], making it a valuable chemopreventive candidate [214, 215]. An experimental condition involving a prototypic tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) TPA-induced NF-κB activation and COX-2 expression in human mammary epithelial (MCF-10A) cells, showed an inhibition of NF-κB and COX-2 by modulating ERK1/2-IKKa and NAK-IKKb signaling pathways [216]. SFN inhibited TNF-α-induced mRNA, and protein expression of VCAM-1 blocked TNF-α-induced degradation of IkBa and suppressed the expression of NF-kB p65 [148]. In human embryonic kidney 293T (HEK293T) cells, the muramyl dipeptide (MDP)-induced activation of NF-κB was inhibited by

Garlic (*Allium sativum* L.) is an important rich source of organosulfur compounds such as allicin, diallyl disulfide (DADS), diallyl trisulfide (DATS) and S-allylmercaptocysteine (SAMC)). Georgia et al. in a well elucidated publication, discussed in details the mechanisms involved in the Cancer Chemoprevention potentials of Garlic Organosulfur. They proposed a model explaining the association between garlic organosulfur compounds and the immune system in carcinogenesis. This model clearly implicated the activities of inflammatory mediators in tumor growth and progression [219]. Recently, allicin exerted an inhibitory effect on the migration of lymphatic endothelial cells, blocked the activation of vascular endothelial growth factor (VEGF) receptor [220], and was identified to be involved in the suppression of chronic myeloid leukemia K562 cell viability as an active component of *Allium roseum* L. [221]. Triple-negative human breast tumor (MDA-MB-231) cells elicited monocyte chemotactic protein-1 (MCP-1/CCL2) which was evoked by TNF-α, was successfully inhibited by the treatment with diallyl disulfide (DADS) [222]. Demonstrating that the administration of DADS can mitigate CCL2-enhanced tumor cell invasion, migration, and proliferation. In the quest to understanding the mechanism of action of the anti-invasive mechanism of DATS in human bladder carcinoma, Dong *et al.* discovered that DATS operated by up-regulating the expression of tissue inhibitor of metalloproteinase (TIMP)-1/2, which consequently blocked the protein and mRNA expressions of matrix metalloproteinase (MMP)-2 and MMP-9 thereby resulting in the suppression of inversion and migration in human bladder carcinoma (5637) cell line [223]. S-allylmercaptocysteine, a water-soluble derivative of garlic recently showed an impres-
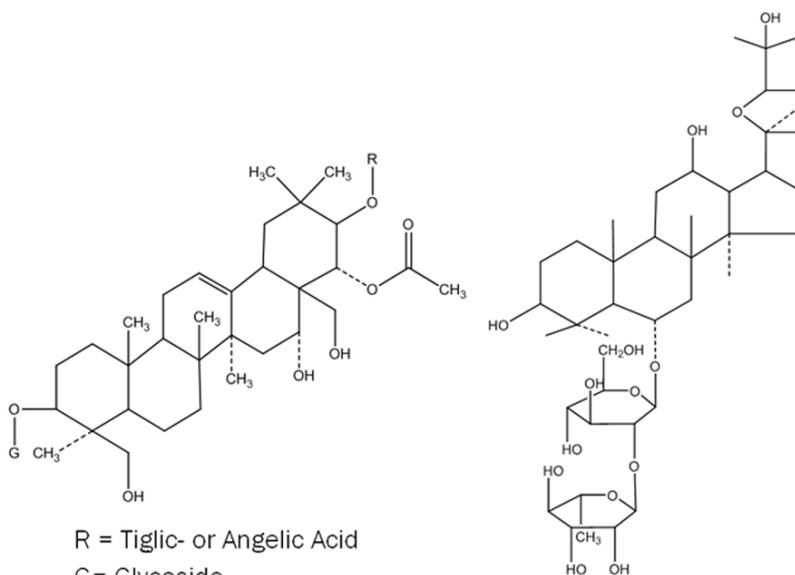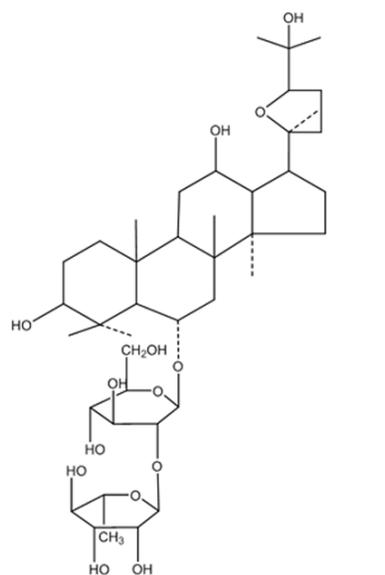
Anti-inflammatory phytochemicals and cancer
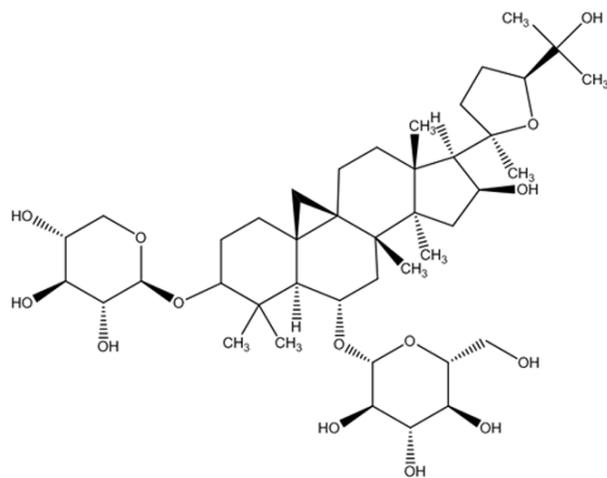
Astagaloside IV (AS-IV)
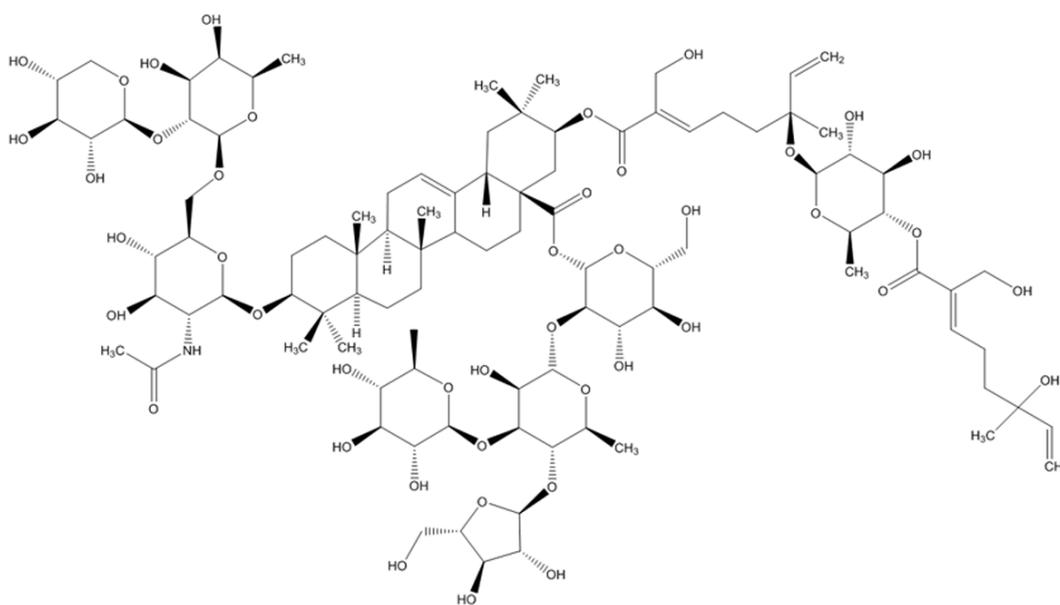
Avicin D

R = Tiglic- or Angelic Acid
G= Glycoside
Beta escin

Pseudoginsenoside-F11

DS-echnoside A

Saikosaponin D

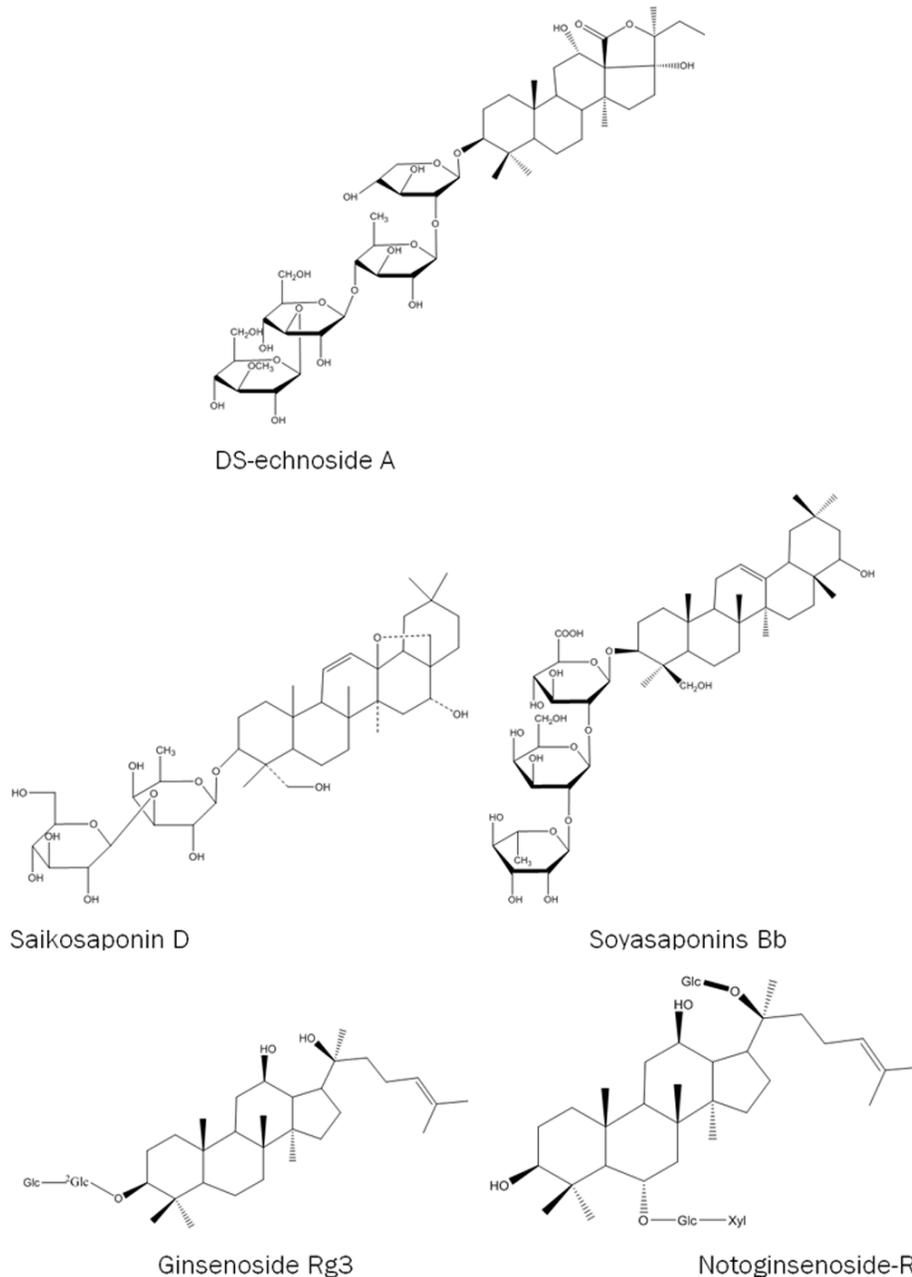Soyasaponins Bb

Ginsenoside Rg3

Notoginsenoside-RI

Figure 5. Chemical structure of saponins. For other chemical structures of saponins in American ginseng and *Panax notoginseng* see [235, 242].

sive anti-cancer effect by suppressing benzo(a) pyrene-induced precancerous carcinogenesis in human lung cells. The experimental data provided evidence of the blocking of nuclear factor-kappa B (NF-κB) activity and reduction of ROS formation by S-allylmercaptocysteine treatment [224].

Saponins

Saponins are amphipathic glycosides. Structurally they have one or more hydrophilic glyco-

side moieties combined with a lipophilic triterpene derivative and are known for their characteristics soap-like foaming activity produced when shaken in aqueous solutions. Over the years, saponins (**Figure 5**) have been reported to have various biological activities including anti-inflammatory and anti-cancer activities. Different saponins, such as Astragaloside IV (AS-IV), Avicin D, β-escin, Ds-echinoside A, Saikosaponin-D, and Soyasaponin Bb, have been reported to impede the growth
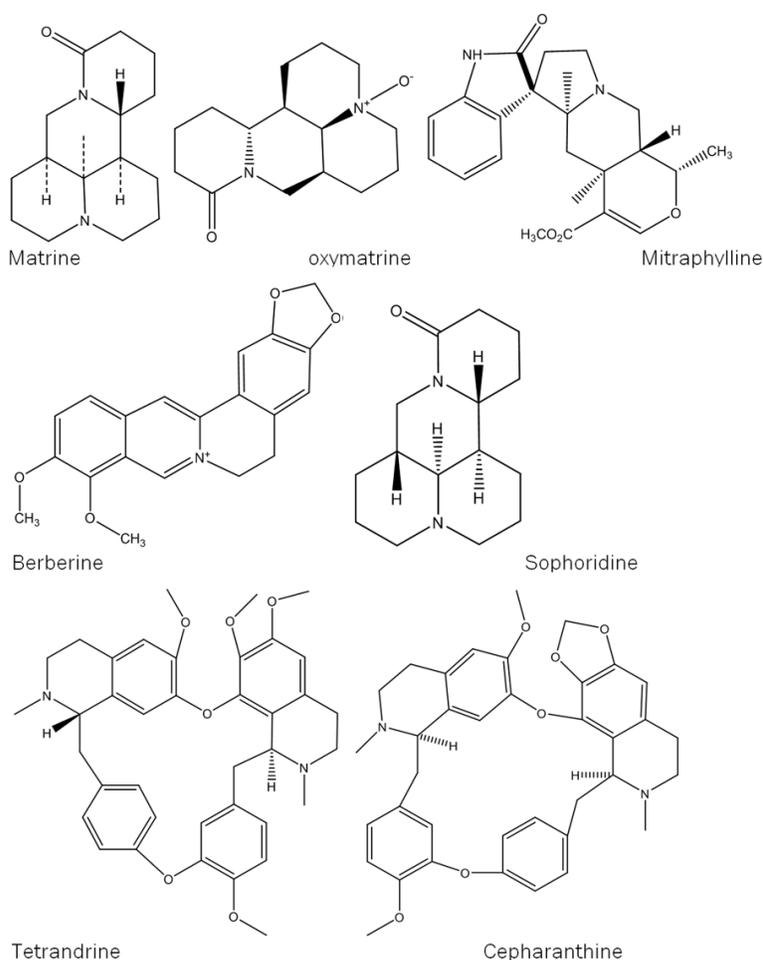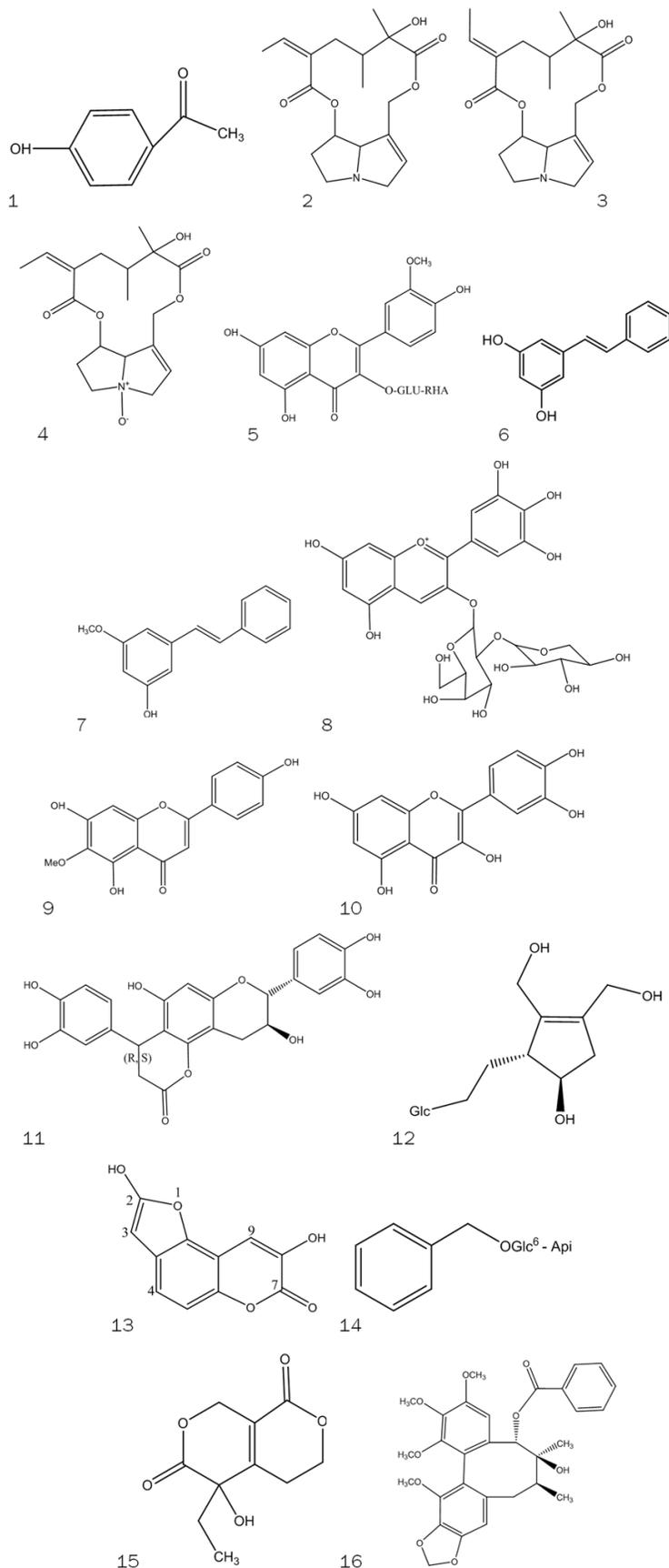
Figure 6. Chemical structure of Alkaloids.

and progression of cancer via the inhibition of inflammatory events [225-230]. Astragaloside IV (AS-IV), from Astragali Radix, was reported to have decreased the levels of MMP-2, MMP-9, integrin β, AS-IV, TGF-β1, TNF-α and IL-6 l, resulting in the suppression of A549 cells migration and invasion. The experiment suggests that AS-IV inhibition of migration and invasion in human lung cancer A549 cells might be connected to the PKC-α-ERK1/2-NF-κB pathway. Presenting AS-IV as a strong candidate for the inhibition of metastasis of human lung cancer [225]. β-escin inhibited NF-κB activation evoked by TNF-α in KBM-5 leukemia cells, and also suppressed the activation of iNOS, STAT1 and STAT3 elicited by interleukin-6 in HepG2, HUH-7, PLC/PRF5 liver cancer cells and A549 lung cancer cells. Moreover, β-Escin reduced the activation of p38 MAPK in A549 cells, which eventually led to the suppression of the induction and proliferation of apoptosis [227, 228, 231]. A study designed to investi-

gate the mechanism-based chemopreventive nature of *Rhizoma Paridis* saponins (RPS) against DEN-induced lung carcinogenesis in Kunming mice, showed the down-regulation of the levels of inflammatory factors, like TNF-α, IL6, COX-2 and the inhibition of NF-κB pathways. Suggesting that RPS would be a promising lung tumor suppressor agent [107]. A triterpenoid saponin from the *Anemone flaccida* was shown to exhibit anti-tumor activities of inducing apoptosis through the inhibition of COX-2/PGE2 pathway [232]. Another triterpenoid saponins isolated from *Gynostemma pentaphyllum*(GpS) was reported to effectively decreased the protein expression of p-STAT3 and the mRNA expression of IL-1β, in *Apc*[Min/+] mice [233]. The production of tumor necrosis factor-α (TNF-α) elicited by Lipopolysaccharide-induced Inflammation in mouse macrophages, was down-regulated by Astragalus saponins (AST). AST also obstructed the phosphorylation of p38 (MAPK), suppressed the degradation IκBα and the activation of nuclear factor NF-κB [234]. American ginseng extract which constitutes ginsenosides (Saponins) showed an inhibitory effect on inflammatory cytokine expressions, such as IL-1a, IL-1b, IL-6, IFN-g, G-CSF, and GM-CSF in azoxymethane/dextran sodium sulfate-induced colon carcinogenesis in mice [235]. Notoginsenoside-R1(NG-R1), the main active ingredient of Panax notoginseng, suppressed the degradation of inhibitor of nuclear factor-κB (NF-κB) α, the activation of NF-κB, inhibited IL-6, IL-1β and TNF-α in H9c2 cardiomyocytes [236]. Ginsenoside Rg3 exhibited remarkable therapeutic effects in human prostate cancer cells (LNCaP, PC3, and DU145) and colon cancer cells (SW620 and HCT116)by inhibiting NF-κB pathway [237-239]. An in vitro study using a microglial cell line N9, Pseudoginsenoside-F11 (a triterpenoid saponin found in American ginseng but not in Asian ginseng) sig-

nificantly suppressed inflammatory mediators such as NO, PGE2, IL-1b, IL-6 and TNF-α [240]. Ds-Echinoside A, a non-sulfated triterpene glycoside, displayed antimetastatic and antiproliferative activity through the inactivation of NF-κB-dependent MMP-9 expression and showed a significant cytotoxic activity with an IC50 of 2.65 µM in HepG2 human hepatocellular carcinoma cells [239]. Platycodon grandiflorum root-derived saponins (Changkil saponins, CKS) mRNA expression of TARC, TNF-α, IFN-γ, IL-4, IL-5, and IL-13 in mice sensitized and challenged with 2,4-dinitrochlorobenzene (DNCB). Moreover, CKS and platycodin D inhibited TNF-α/IFN-γ-induced TARC expression through the suppression of NF-κB and STAT1 and the induction of Nrf2/ARE-mediated hemeoxygenase-1 (HO-1) expression in cells [241]. *Panax notoginseng* decreased the expression of iNOS and COX-2 in the azoxymethane (AOM)/dextran sulfate sodium (DSS) mouse model, suggesting the usefulness of *P. notoginseng* in the prevention and treatment of colitis and inflammation-associated colon carcinogenesis [242]. Additionally, *P. polyphylla* Smith var. *chinensis* (Franch.) exerted anti-lung cancer activities by decreasing the expressions of inflammatory cytokines such as TNF-α, IL-8, MCP-1, IL-6, and TGF-β1, as well as cell adhesion molecule ICAM-1. Thereby inhibiting tumor growth in C57BL/6 mice and A549 Cell Line [121].

Alkaloids

Alkaloids are organic compounds that contain nitrogen (**Figure 6**). Many alkaloids ha-

18: R₁ = R₂ = OCH₃, R₃ = H
19: R₁ = OH, R₂ = OCH₃, R₃ = H
20: R₁ = R₂ = OH, R₃ = OCH₃

22: R₁ = R₂ = OH, R₃ = H
23: R₁ = R₂ = R₃ = OH
24: R₁ = R₂ = OAc, R₃ = H

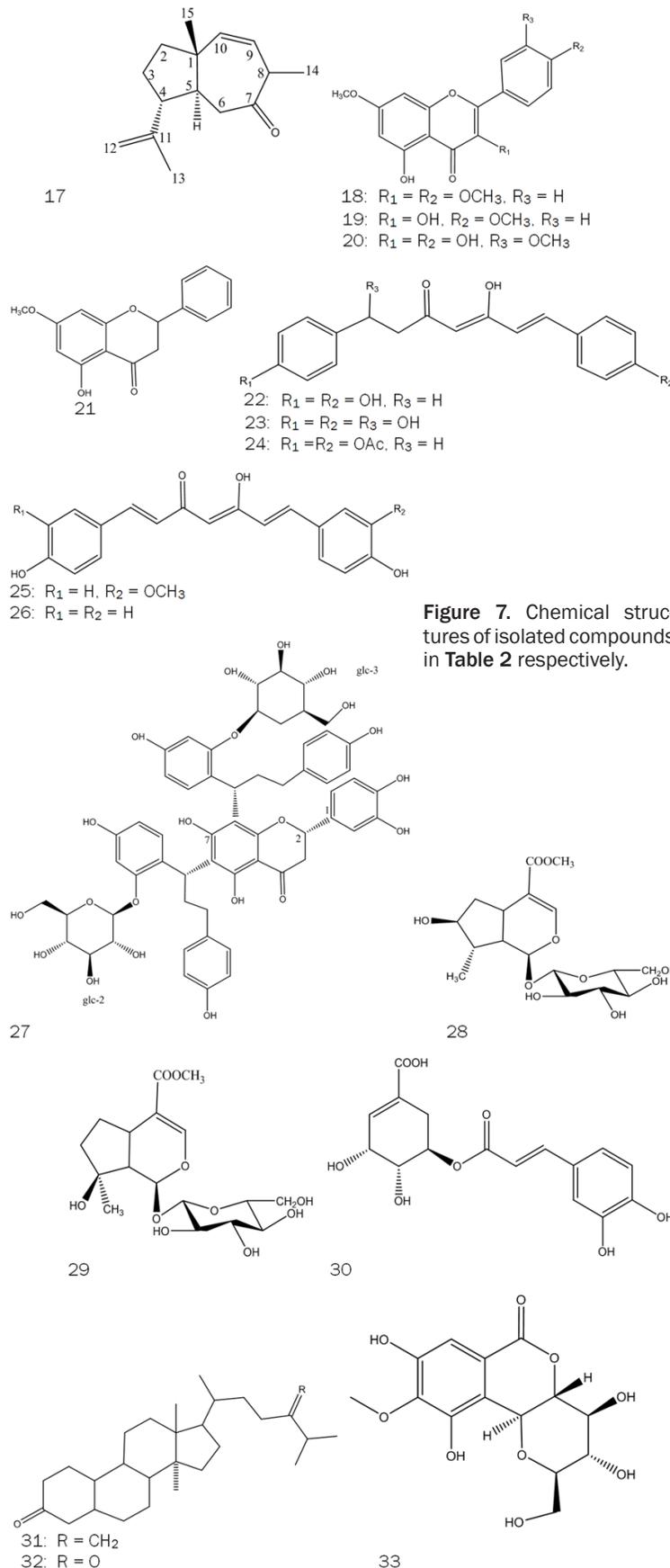25: R₁ = H, R₂ = OCH₃
26: R₁ = R₂ = H

Figure 7. Chemical structures of isolated compounds in **Table 2** respectively.

31: R = CH₂
32: R = O

ve heterocyclic rings as a part of their structure and are basic ("alkaline", due to an unshared pair on N). Most alkaloids are spectacularly physiologically active and are widely used for medicinal purposes. A mixture of natural compounds extracted from two medicinal herbs: Kushen (Radix *Sophorae flavescentis*) and Baituling (Rhizoma *Smilacis glabrae*) known as Compound Kushen Injection (CKI), has long been used for the inflammation and solid tumors [243]. It consists of mainly alkaloids such as matrine, oxymatrine and sophoridine [243, 244] An investigation of the effect of fufang Kushen Injection Liquid (FF-KSIL) on gastric immunity and oxidant-antioxidant during *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)-induced gastric carcinogenesis revealed a decrease in the serum levels of IL-6 and TNF-α [245]. Matrine, a quinolizidine alkaloid found in plants from *Sophora* genus, ameliorates LPS-induced intestinal inflammation in mice by mediating the release of the inflammatory mediator NO [246]. Moreover, matrine significantly reduced the protein expressions of TNF-α and IL-6 in a mouse model of vincristine-Induced neuropathic pain and impeded TNF-a-induced expression of IL-6 and adhesion molecules in airway epithelial cells [247, 248]. Matrine also demonstrated anti-inflammatory effect on airway inflammation by inhibiting the expression of suppressor of cytokine signaling 3 (SOCS-3) through the inhibition of NF-kB signaling in airway epithelial cells and asthmatic mice [248]. In LPS-treated mice

and Caco-2 cells, matrine significantly down-regulated the expression of pro-inflammatory cytokines such as IL-1β and thereby resolved LPS-induced inflammation and oxidative stress [249]. Besides, matrine demonstrated an inhibitory effect on the invasion and migration of castration-resistant prostate cancer cells, by decreasing the expression levels of matrix metalloproteinase (MMP)-9 and MMP-2 through the inhibition of NF-κB signaling pathway [250]. Mitraphylline (MTP) an active alkaloid in the leaves *Mitragyna speciosa* and the major pentacyclic oxindolic alkaloid present in *Uncaria tomentosa*, markedly suppressed the activation of pro-inflammatory cytokines such as IL-6 and IL-8 and TNF-α in LPS-challenged neutrophils [251]. Bisbenzylisoquinoline alkaloid-tetrandrine has been known for its remarkable inhibition of ILs, TNF-a, prostaglandin, COX-2 in and other pro-inflammatory mediators [252-254]. Making it an attractive mediator of cancer-related inflammation. Berberine a benzylisoquinoline alkaloids found in plants such as the genus Berberis, *Eschscholzia californica* (Californian poppy), *coptis chinensis* (chinese goldthread) and *Phellodendron amurense* (Amur cork tree) was reported to have alleviated *in vitro* and *in vivo* inflammation and modulated the metastasis of human melanoma cancer cells via the inhibition of NF-κB, cox-2, prostaglandin E2 and prostaglandin E2 receptors [255]. In addition, berberine-treated hepatocellular carcinoma (HCC) cells showed a decreased expression of COX-2, MMP-9, NF-κB and urokinase-type plasminogen activator (uPA), which consequently led to the suppression of invasion and migration of HCC [256]. This possibly denotes that berberine exerted its anti-cancer effect through the modulation of inflammation-associated pathways. Another isoquinoline, Cepharanthine(CEP) a bisbenzylisoquinoline alkaloid found in the plant *Stephania cepharantha* was shown to inhibit nitric oxide (NO) production, the expression of iNOS, MAPK, COX-2 and NF-κB in RAW264.7 cells [257]. CEP inhibiton of MMP-9 expression was said to have prevented the degradation of extracellular matrix (ECM) component [257]. Implying that CEP could be useful for anti-cancer therapy, owing to its ability to mediate inflammation and inhibit proliferation and migration in vascular smooth muscle cells (VSMC) [257].

Conclusion

Despite the emergence of synthetic compounds, the role of natural product in drug discovery cannot be underestimated; as they can be useful as bioactive phytochemicals or serve as a guideline to synthetic and medicinal chemists who modifies the structures to induce various Pharmacologi-cal activities. A series of natural products, such as paclitaxel, vinblastine, camptothecin, and etoposide, have been successfully included in the standard repertoire of cancer chemotherapy. Interestingly, paclitaxel, vinblastine, and etoposide were also included in the 19th WHO Model List of Essential Medicines (April 2015) [258]. Among the numerous syntheses of Camptothecin (CPT) developed by synthetic and medicinal chemists, Two CPT analogs irinotecan and topotecan are used in cancer chemotherapy today [259-261]. Therefore, there is a possibility that the above discussed plant extracts and phytochemicals can provide potential anti-cancer drug candidates; since they were able to modulate the inflammatory mediators in cancer (**Figure 2**). Moreover, due to the pleiotropic activities demonstrated by most of these plant products; by inhibiting more than one of the key inflammatory factors and in turns inhibiting the formation and progression of cancer. They may provide a more efficient chemopreventive and chemotherapeutic agents with less toxicity. However, further studies are required to translate the above discussed natural products into clinical use, and at this point in Cancer research all stones need to be unturned, who knows? The least expected approach might end up becoming a way.

Disclosure of conflict of interest

None.

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