Expert Opinion

1. Introduction
2. Major targets in cancer therapy
3. Ayurvedic concept of cancer
4. Source of anticancer drugs from Ayurvedic medicine
5. Ayurvedic agents as chemosensitisers and radiosensitisers
6. Herb–drug interactions
7. Expert opinion
8. Conclusions

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From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer

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Cancer is a hyperproliferative disorder that involves transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis and metastasis. Extensive research during the last 30 years has revealed much about the biology of cancer. Drugs used to treat most cancers are those that can block cell signalling, including growth factor signalling (e.g., epidermal growth factor); prostaglandin production (e.g., COX-2); inflammation (e.g., inflammatory cytokines: NF-κB, TNF, IL-1, IL-6, chemokines); drug resistance gene products (e.g., multi-drug resistance); cell cycle proteins (e.g., cyclin D1 and cyclin E); angiogenesis (e.g., vascular endothelial growth factor); invasion (e.g., matrix metalloproteinases); antiapoptosis (e.g., bcl-2, bcl-X_L, XIAP, survivin, FLIP); and cellular proliferation (e.g., c-myc, AP-1, growth factors). Numerous reports have suggested that Ayurvedic plants and their components mediate their effects by modulating several of these recently identified therapeutic targets. However, Ayurvedic medicine requires rediscovery in light of our current knowledge of allopathic (modern) medicine. The focus of this review is to elucidate the Ayurvedic concept of cancer, including its classification, causes, pathogenesis and prevention; surgical removal of tumours; herbal remedies; dietary modifications; and spiritual treatments.

Keywords: apoptosis, Ayurvedic medicine, cancer, inflammation, metastasis

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1. Introduction

According to the International Agency for Research on Cancer (IARC), in 2002, cancer killed > 6.7 million people around the world; another 10.9 million new cases were diagnosed; and at the current rate, an estimated 15 million people will be diagnosed annually by 2020. Cancer is one of the leading causes of death in the US and around the world. Several chemotherapeutic, cytotoxic and immunomodulating agents are available in Western medicine to treat cancer. Besides being enormously expensive, these drugs are associated with serious side effects and morbidity. Still, the search continues for an ideal treatment that has minimal side effects and is cost-effective. Today, in Western medicine, only a limited number of plant products are being used to treat cancer. However, some of the widely used anticancer drugs, such as taxol and vinca alkaloids, are obtained from medicinal plants. This review focuses on the ancient perspective of cancer and how it can be integrated

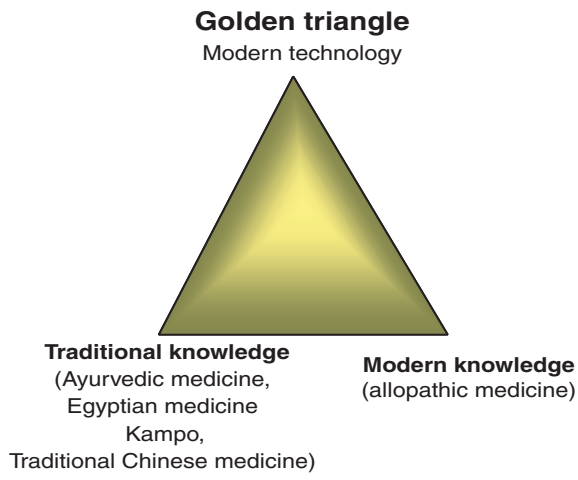

Figure 1. Relationship between Ayurveda and modern medicine.

with modern science for the best treatment of cancer (**Figure 1**). Ayurveda, one of the major traditional forms of medical practice in India, has produced many useful leads in developing medications for chronic diseases. Almost 25 centuries ago, Hippocrates proclaimed, 'Let food be thy medicine and medicine be thy food.' According to a recent report by Newman *et al.*, as many as 65% of formally synthetic hypertension drugs are plant based [1].

Of the 121 prescription drugs in use today for cancer treatment, 90 are derived from plants. Almost 74% of these, including taxol, were discovered by investigating a folklore claim [2,3]. Between 1981 and 2002, 48 out of 65 drugs approved for cancer treatment were natural products, based on natural products, or mimicked natural products in one form or another [1]. These phytochemicals are commonly called chemotherapeutic or chemopreventive agents. Phytochemicals may fight disease through suppression of the inflammatory response. Dysregulated inflammation contributes to many diseases, including cancer [4,5]. It stands to reason then, that suppression of inflammation, whether by phytochemicals or other means, should delay the onset of disease [2,3].

Tumourigenesis is a multistep process that begins with cellular transformation, progresses to hyperproliferation and culminates in the acquisition of invasive potential and angiogenic properties and the establishment of metastatic lesions [6]. This process can be activated by any of various environmental carcinogens (such as cigarette smoke, industrial emissions, gasoline vapors), inflammatory agents (such as TNF and H_2O_2), tumour promoters (such as phorbol esters and okadaic acid). This multistep process of carcinogenesis involves three phases: tumour initiation, promotion and progression.

Several population-based studies indicate that people in Southeast Asian countries have a much lower risk of developing colon, gastrointestinal, prostate, breast and other cancers when compared with their Western counterparts. It is likely that dietary constituents, such as garlic, ginger, soya, curcumin, onion, tomatoes, cruciferous vegetables, chilies and green tea, play an important role in protection from these cancers. These dietary agents are believed to suppress the transformative, hyperproliferative and inflammatory processes that initiate carcinogenesis. Their inhibitory influences may ultimately suppress the final steps of carcinogenesis as well, namely angiogenesis and metastasis. These dietary constituents have been classified as chemopreventive agents, and their ability to delay the onset of carcinogenesis has been studied extensively. Because these chemopreventive agents are derived from natural sources, they are considered pharmacologically safe. The current review, although brief, evaluates the untapped therapeutic potential of these agents in the setting of several molecular targets that are currently under investigation.

2. Major targets in cancer therapy

Within the last 50 years, major advances have been made in our understanding of the basic biology of cancer. One important advance is the understanding that suppression of certain cell signalling pathways can suppress tumourigenesis. These signalling pathways are discussed below.

2.1 Role of the NF-κB activation pathway in tumourigenesis

NF-κB is a family of closely related protein dimers that bind to a common sequence motif in DNA called the κB site [7]. The molecular identification of its p50 subunit (v-REL) as a member of the reticuloendotheliosis (REL) family of viruses provided the first evidence that NF-κB is linked to cancer. Research over the past decade has revealed that NF-κB is an inducible transcription factor for genes involved in cell survival, cell adhesion, inflammation, differentiation and growth. In most resting cells, NF-κB is sequestered in the cytoplasm by binding to the inhibitory IκB proteins that block the nuclear localisation sequences of NF-κB. NF-κB is activated by a variety of stimuli, such as carcinogens, inflammatory agents, and tumour promoters, including cigarette smoke, phorbol esters, okadaic acid, H_2O_2 and TNF. These stimuli promote dissociation of IκBα through phosphorylation, ubiquitinylation and its ultimate degradation in the proteasomes. This process unmasks the nuclear localisation sequence of NF-κB, facilitating its nuclear entry, binding to κB regulatory elements and activation of transcription of target genes. Many of the target genes that are activated are critical to the establishment of the early and late stages of aggressive cancers, including expression of cyclin D1, apoptosis suppressor proteins such as bcl-2 and bcl-X_L and those required for metastasis and angiogenesis, such as matrix metalloproteases (MMPs) and vascular endothelial growth factor (VEGF).

2.2 Role of the AP-1 activation pathway in cancer prevention

Activated protein-1 (AP-1) is another transcription factor that regulates the expression of several genes involved in cell differentiation and proliferation. Functional activation of the AP-1 transcription complex is implicated in tumour promotion as well as in malignant transformation. This complex consists of either homo- or heterodimers of the members of the JUN and FOS family of proteins [8]. This AP-1-mediated transcription of several target genes also can be activated by a complex network of signalling pathways that involve external signals such as growth factors, mitogen-activated protein kinases (MAPKs), extracellular signal-regulated protein kinases and c-jun N-terminal kinase (JNK). Some of the target genes activated by the AP-1 transcription complex mirror those activated by NF-κB and include cyclin D1, bcl-2, bcl-X_L, VEGF, MMP and urokinase plasminogen activator (uPA). Expression of genes such as MMP, and especially uPA, promotes angiogenesis and invasive growth of cancer cells. Most importantly, AP-1 can also promote the transition of tumour cells from an epithelial to a mesenchymal morphology, one of the early steps in tumour metastasis. These oncogenic properties of AP-1 are primarily dictated by the dimer composition of the AP-1 family proteins and their post-transcriptional and translational modifications.

2.3 Role of proliferation and apoptosis in tumourigenesis

Several reports have been published in the past eight years showing that activation of NF-κB promotes cell survival and proliferation, and downregulation of NF-κB sensitises the cells to apoptosis. The mechanism through which NF-κB promotes these proliferation and cell survival mechanisms has become increasingly clear. Expression of several genes, including bcl-2, bcl-X_L, inhibitor-of-apoptosis protein (IAP), survivin, cyclin D1, TNF receptor-associated factor 1(TRAF1), and TRAF2, has been reported to be upregulated by NF-κB [9]. The proteins coded by these genes function primarily by blocking the apoptosis pathway. Several studies have demonstrated that NF-κB activation promotes cell survival and proliferation mechanisms and that suppression of NF-κB leads to abrogation of these mechanisms. Similarly, c-JUN is primarily a positive regulator of cell proliferation because c-jun-deficient fibroblasts have a marked proliferation defect *in vitro* and *in vivo*. c-jun protein, once fully activated by JNK kinases, induces transcription of the positive regulators of cell cycle progression, such as cyclin D1, and represses the negative regulators, such as the tumour suppressor p53 and the cyclin-dependent kinase inhibitor p16 (INK4A). Moreover, activated and oncogenic AP-1 can antagonise apoptosis in several tumours.

2.4 Growth factor activation pathway in tumourigenesis

The potent cell proliferation signals generated by various growth factor receptors, such as the epidermal growth factor receptor, insulin-like growth factor-1 receptor and VEGF receptor networks, constitute the basis for receptor-driven tumorigenicity in the progression of several cancers [6]. The consequence of these abnormal growth factor receptor signalling pathways include increased cell proliferation, suppression of apoptotic signals (especially under anchorage-independent conditions), and an increase in the tumour's invasive behaviour, which contributes to metastatic spread and the growth of new blood vessels. Several chemopreventive phytochemicals, including curcumin, genistein, resveratrol and catechins, recently have been shown to be powerful inhibitors of several growth factor receptors, including epidermal growth factor receptor (EGFR). Some of these phytochemicals, such as curcumin, also have the capacity to inhibit the ligand-stimulated activation of the EGFR, indicating that they have the potential to break the autocrine loops that are established in several advanced cancers [10]. The inhibitory actions of these phytochemicals have several other potential advantages in treating patients with late-stage cancers. A blockade of EGFR, for example, may predispose the cancer cells to apoptosis. Moreover, inhibition of EGFR disables the protein's capacity to provide the cancer cell the matrix-independent survival support it needs to expand and acquire invasive potential. Third, these chemopreventive chemicals function by inhibiting other tyrosine kinases, such as *c-src,* that are involved in the activation of the G-protein-coupled receptor to the transactivation of EGFR, as occurs extensively in established cancers. Finally, most of these phytochemicals also inhibit, by a similar mechanism, the HER2/*neu* receptor, which is overexpressed in breast, prostate, ovarian and lung cancers. Curcumin has been shown not only to inhibit the tyrosine kinase activity of this receptor, but also to deplete the protein itself. It does so by interfering with the function of the ATP-dependent GRP94 chaperone protein, which is involved in maintaining the properly folded state of the receptor [11]. Moreover, by inhibiting HER2/neu, most of these phytochemicals also can interfere with the cross-talk between the receptor and the estrogen receptor pathways in these cancers. Thus, they may be beneficial in treating hormone-resistant breast cancer patients by restoring their hormone responsiveness.

2.5 Role of the JAK–STAT pathway in tumourigenesis

Although cancer arises through several genetic or epigenetic mechanisms that contribute to a number of abnormal oncogenic signalling pathways, all seem to converge on a very limited number of nuclear transcription factors that function as final effectors, triggering specific gene expression patterns for a particular cancer. These belong to the canonical signal transducers and activators of transcription (STAT) family of proteins [12]. They can be activated by phosphorylation through janus kinase (JAK) or cytokine receptors, G-protein-coupled receptors or growth factor receptors (such as EGFR); by platelet-derived growth factor receptors that have intrinsic tyrosine kinase activity; or by intracellular nonreceptor tyrosine kinase recruitment. Of the seven STAT proteins identified so far,

constitutive activations of STAT3 and STAT5 have been implicated in multiple myeloma, lymphomas, leukaemias and several solid tumours, making these proteins logical targets for cancer therapy. These STAT proteins contribute to cell survival and growth by preventing apoptosis through increased expression of antiapoptotic proteins, such as bcl-2 and bcl-X_L. Recently, STAT 3 was shown to be a direct activator of the VEGF gene, which is responsible for increased angiogenesis. More importantly, the increased expression of STAT3 and STAT5 transcription factors is crucially involved in the processes through which tumours evade immunological surveillance by increasing the expression of immune-suppressing factors and decreasing the expression of pro-inflammatory cytokines that are responsible for the maturation of the dendritic cells [13].

2.6 Role of multi-drug resistance in tumourigenesis

MDR in human cancer is often associated with overexpression of the mdr-1 gene, which encodes a 170 kDa transmembrane protein, termed P-glycoprotein (P-gp). P-glycoprotein is considered to be of prognostic relevance in different tumour types. It is involved in resistance to natural product-based chemotherapeutics, including taxanes, anthracyclines, vinca alkaloids, podophyllotoxins and camptothecins. Although several reports suggest that P-170 is clinically relevant in haematological malignancies, its role in solid tumours is not well understood. Its overexpression has been found to be correlated with the poor outcome observed in patients treated with chemotherapy and presenting drug resistance. Activation of the MDR-1 gene or selection of intrinsically MDR neoplastic cells may occur at early stages of tumourigenesis of oral cancers, before the real evidence of cellular transformation [14]. Thus, the contact with possible chemical carcinogens, such as those of tobacco smoke, may induce activation of MDR-1 gene. MDR-1 product expression in oral squamous cell carcinoma might suggest that an overexpression of this protein could constitute a hallmark of potential more aggressive phenotype for this type of neoplasia.

Quantitative flow-cytometric analysis of P-gp expression showed a significant increase in P-gp levels in untreated primary oral tumours and in dysplastic lesions as compared with normal oral tissues. A marked significant increase in P-gp expression was observed in recurrent oral carcinomas as compared with normal oral tissues and dysplastic lesions. Among recurrent tumours, a significant increase in the level of P-gp was observed in T4-stage tumours as compared with T3-stage tumours. Thus, P-gp is differentially expressed during oral tumourigenesis, and may be an indicator of the biological behaviour of oral malignancies [15]. Activation of MDR-related gene expression also occurs during the tumourigenesis of urothelial cancers and that it may confer *de novo* and acquired drug resistance on urothelial cancers [16]. Like cytochrome P450s (CYP3A4), P-gp is vulnerable to inhibition, activation or induction by herbal constituents.

2.7 Role of COX-2 in tumourigenesis

Numerous preclinical studies point to the importance of regulating cyclooxygenase-2 (COX-2) expression in the prevention and, most importantly, treatment of several malignancies. This enzyme is overexpressed in practically every premalignant and malignant condition involving the colon, liver, pancreas, breast, lung, bladder, skin, stomach, head and neck and oesophagus [17]. COX-2 overexpression is a consequence of the deregulation of transcriptional and post-transcriptional control. Several growth factors, cytokines, oncogenes and tumour promoters stimulate COX-2 transcription. Expression of COX-2 is increased in HER2/neu-expressing breast carcinomas owing to enhanced *ras* signalling. Depending upon the stimulus and the cell type, different transcription factors, including AP-1, NF-IL-6, and NF-κB, can stimulate COX-2 transcription [17]. Wild-type p53 protein expression can suppress COX-2 transcription, whereas the mutant p53 protein cannot. Consistent with this observation, increased COX-2 levels are seen in several epithelial cancers that express mutant p53. Taken together, these findings suggest that the balance between the activation of oncogenes and the inactivation of tumour suppressor genes and the expression of several pro-inflammatory cytokines can modulate the expression of COX-2 in tumours. Complicating matters further is the fact that conventional cancer therapies such as radiation and chemotherapy can induce COX-2 and prostaglandin biosynthesis. Thus, inhibition of this enhanced COX-2 activity in tumours clearly has therapeutic potential.

2.8 Role of angiogenesis in tumourigenesis

Angiogenesis, the regulated formation of new blood vessels from existing ones, is the basis of several physiological processes, such as embryonic development, placenta formation and wound healing. It is one of the best examples of how a tumour can take control of these processes and deregulate them to its advantage. In the normal and orderly formation of new blood vessels, the endothelial cell receives the stimulatory signal and secretes MMP and heparanase, which cause the extracellular matrix to dissolve. The tight junction between the endothelial cells is then altered, and the cells project through the newly created space where newly formed endothelial cells organise into fresh capillary tubes. This allows the sprouting vessel to grow toward the source of fresh blood [18]. When a tumour tries to grow new blood vessels, most of these normal physiological rules governing new blood vessel growth are subverted. Blood vessels newly formed by tumours often have incomplete basement membranes, and the microvasculature is often chaotic, following convoluted paths without organisation. These vessels also have a disproportionate ratio of endothelial cells to pericytes and abnormal pericyte coverage. The new blood vessels are hyperpermeable because of an imbalance of pro- and antiangiogenic factors, and they are often leaky [18]. Moreover, tumour cells themselves try to mimic the properties of endothelial cells and form a loose vasculogenic meshwork by processes such as vessel

cooption and vasculogenic mimicry [19]. Thus, interference with the mechanisms of angiogenic switch, vessel cooption and vasculogenic mimicry will be of great therapeutic value in several advanced cancers.

2.9 Role of cyclins in tumourigenesis

Hundreds of types of cancer exhibit global changes in gene expression, but only a very small number of crucial alterations are common to all tumours. These common alterations are related to those that disrupt the normal cell cycle control checkpoints. The retinoblastoma and tumour suppressor p53 proteins that are crucial for these controls are usually lost in several cancers. The central role of the G_1 to S and the G_2 to M transitions and the corresponding checkpoints in cancer development are well established [20]. Formation and regulation of enzyme complexes with the D-type cyclins and their partners and the B-type cyclins with their associated proteins are particularly well characterised, as is the control of retinoblastoma function by phosphorylation.

3. Ayurvedic concept of cancer

Charaka and Sushruta Samhita (700 BC) both described the equivalent of cancer as granthi (benign or minor neoplasm) and arbuda (malignant or major neoplasm) [21-23]. Both can be inflammatory or non-inflammatory, based on the doshas involved [24]. The term dosha describes the three principles that govern the psychophysiological response and pathological changes in the body. The balanced coordination of these three systems (Vata, Pitta and Kapha) in body, mind and consciousness is the Ayurvedic definition of health [25]. The fundamental theory of Ayurvedic treatment is based on restoration of the balance between these three major bodily systems. Tridoshic tumours are usually malignant because all three major body humors lose mutual coordination, resulting in a morbid condition [26,27].

Ayurvedic classification of neoplasms depends upon various clinical symptoms in relation to tridoshas.

- Group I: Diseases that can be named as clear malignancies, including arbuda and granthi, such as mamsarbuda (sarcomas) and raktarbuda (leukaemia), mukharbuda (oral cancer), and asadhya vrana (incurable or malignant ulcers).
- Group II: Diseases that can be considered as cancer or probable malignancies, such as ulcers and growths. Examples of these are mamsaja oshtharoga (growth of lips), asadhya galganda (incurable thyroid tumour), tridosaja gulmas, asadhya udara roga, (abdominal tumours like carcinomas of the stomach and liver or lymphomas).
- Group III: Diseases with the possibility of malignancy, such as visarpa (erysipelas), asadhya kamala (incurable jaundice), asadhya pradara (intractable leukorrhea) and tridosaja nadi vrana (intractable sinusitis).

4. Source of anticancer drugs from Ayurvedic medicine

Some of the herbs commonly used in Ayurveda are listed in **Table 1** and **Figures 3**, **4** and **5**. The active components of these herbs, which have anticancer activity, and their molecular targets are described below (**Tables 2**, **3** and **4**, **Figures 2** and **3**).

4.1 Guggulsterone (*Commiphora mukul*)

Guggulsterone [4,17(20)-pregnadiene-3,16-dione] is a plant sterol derived from the gum resin (*guggulu*) of the tree *Commiphora mukul.* The resin has been used in Ayurvedic medicine for centuries to treat a variety of ailments, including obesity, bone fractures, arthritis, inflammation, cardiovascular disease and lipid disorders [28,29]. The antiarthritic and anti-inflammatory activities of gum guggul were demonstrated as early as 1960 by Gujral *et al.* [30]. Sharma *et al.* showed guggul's activity in experimental arthritis induced by a mycobacterial adjuvant [31]. The effectiveness of guggul for treating osteoarthritis of the knee also has been demonstrated [32]. Recent studies have shown that guggulsterone is an antagonist for the bile acid receptor farnesoid X receptor [33,34]. Other studies have shown that guggulsterone enhances transcription of the bile salt export pump [35], thereby regulating cholesterol homeostasis.

An understanding of the molecular mechanisms underlying guggulsterone is just now emerging. In 2003, Meselhy *et al.* showed that guggulsterone can suppress inflammation by inhibiting inducible nitric oxide synthetase (iNOS) expression induced by lipopolysaccharide in macrophages [36]. Because most inflammatory diseases are mediated through the activation of NF-κB, a nuclear transcription factor [7,37], the authors hypothesise that it is involved in guggulsterone's activity.

Guggulsterone suppresses DNA binding of NF-κB induced by TNF, phorbol ester, okadaic acid, cigarette smoke condensate, hydrogen peroxide, and IL-1. Guggulsterone also suppressed the constitutive NF-κB activation expressed in most tumour cells. In addition, guggulsterone decreases the expression of gene products involved in antiapoptosis (IAP1), X chromosome-linked IAP, Bfl-1/A1, bcl-2, cFLIP and survivin), proliferative genes (cyclin D1, c-myc) and metastatic genes (MMP-9, COX-2 and VEGF). This correlated with the enhanced apoptosis induced by TNF and chemotherapeutic agents [38].

4.2 Curcumin (*Curcuma longa*)

Curcumin (diferuloylmethane) is an active component of turmeric (*Curcuma longa*), which has been used as a spice and as an Ayurvedic medicine for centuries on the Indian subcontinent. Curcumin has been shown to suppress carcinogenesis of the skin, liver, lung, colon, stomach and breast. It has also been shown to inhibit the proliferation of a wide variety of tumour cells in culture and to promote apoptosis through Bid cleavage, cytochrome c release, caspase-9 activation and then caspase-3 activation [39-60].

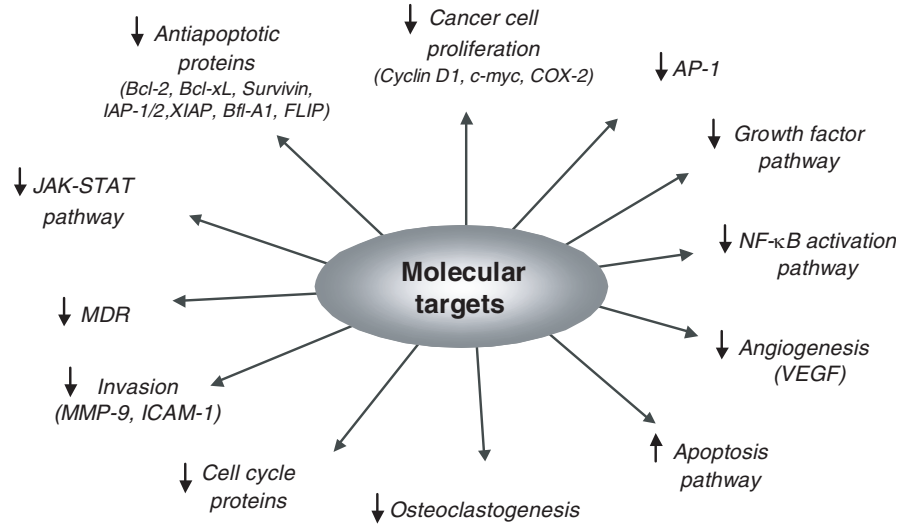

Figure 2. Molecular targets of Ayurvedic drugs.

AP: Activated protein; COX: Cyclooxygenase; IAP: Inhibitor of apoptosis protein; ICAM: Intercellular cell adhesion molecule; JAK: Janus kinase; MDR: Multi-drug resistance; MMP: Matrix metalloprotease; NF-κB: Nuclear factor kappaB; STAT: Signal transducer and activator of transcription; VEGF: Vascular endothelial growth factor; XIAP: X-linked inhibitor of apoptosis.

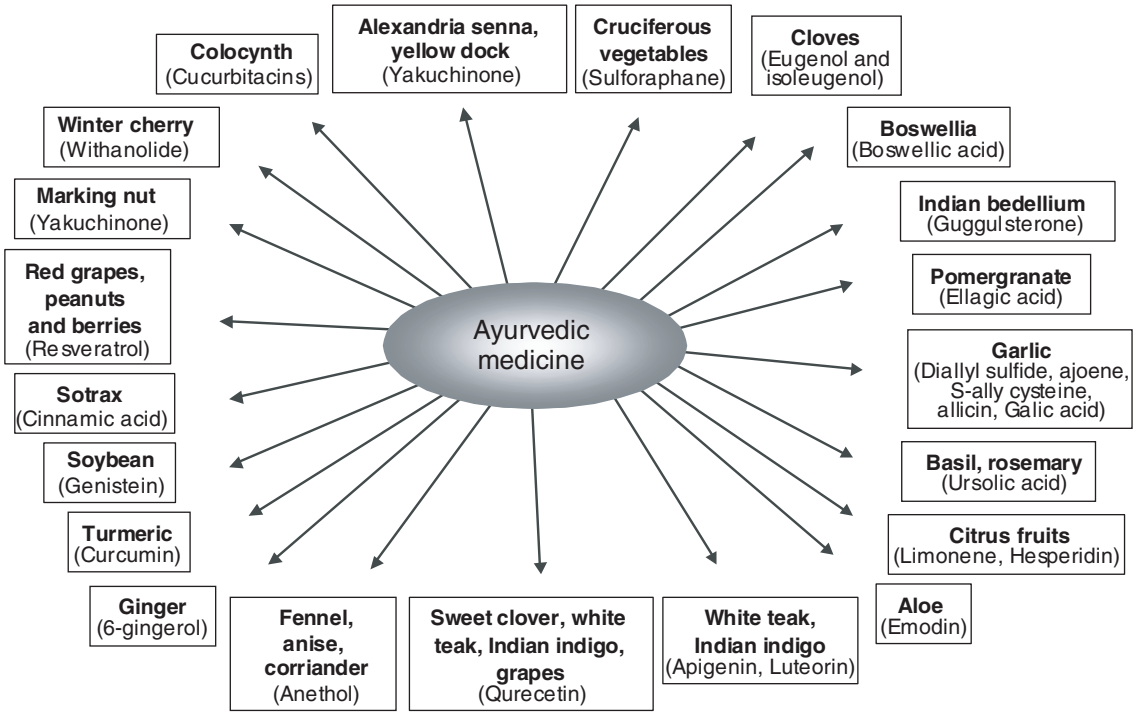

Figure 3. Active components from Ayurvedic medicine.

Curcumin has been shown to lower blood cholesterol, promote wound healing, prevent skin wrinkling, inhibit inflammation, suppress rheumatoid arthritis and inhibit human immunodeficiency virus replication. Curcumin mediates this wide variety of therapeutic effects by regulating the transcription factors NF-κB and activator protein, suppressing IκBα kinase and c-Jun N-terminal kinase, and inhibiting expression of COX-2, cyclinD1, adhesion molecules, MMPs, iNOS, HER2, EGFR, bcl-2, bcl-X_L and TNF. Pharmacologically, curcumin is quite safe, and doses as high as 8 grams per day have been

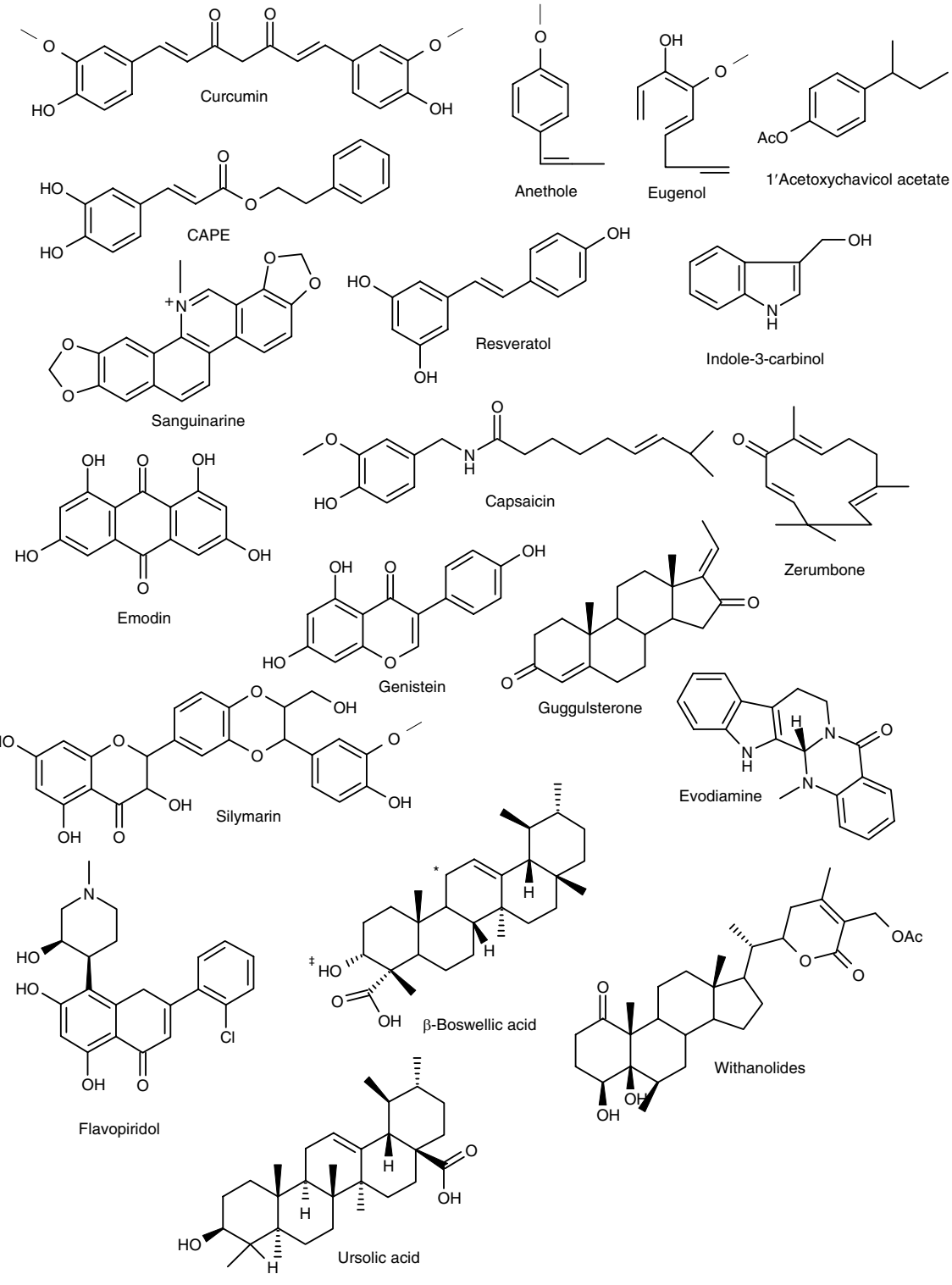

Figure 4. Chemical structures of selected active components in Ayurvedic plants.
*Can have a ketone group: 11-keto-β-boswellic acid. ‡Can be acetylated: Acetyl-β-boswellic acid. Both modifications together, result in acetyl-11-keto-β-boswellic acid.

Figure 5. Sources of Ayurvedic drugs.

administered orally to humans with no side effects. The numerous therapeutic activities of curcumin, its pharmacological safety and its colour qualifies it as 'Indian solid gold'.

Extensive research over the last 50 years has indicated that curcumin can both prevent and treat cancer. Curcumin's anticancer potential stems from its ability to suppress the proliferation of a wide variety of tumour cells; downregulate transcription factors NF-κB, AP-1 and Egr-1; downregulate the expression of COX-2, LOX, iNOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; downregulate growth factor receptors (such as EGFR and HER2); and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. In several systems, curcumin has been shown to be a potent antioxidant and anti-inflammatory agent. Further evidence suggests that curcumin can suppress tumour initiation, promotion and metastasis. Human clinical trials have indicated no dose-limiting toxicity when curcumin is administered at doses up to 10 grams per day. All these studies suggest that curcumin has enormous potential in the prevention and treatment of cancer.

4.3 Resveratrol (*Vitis vinifera*)

The history of resveratrol can be traced back thousands of years. Perhaps the first known use of grape extracts for human health occurred > 2000 years ago in 'darakchasava,' a well-known Indian herbal preparation whose main ingredient is *Vitis vinifera* L. This 'Ayurvedic' medicine is prescribed as a cardiotonic and also is given for other disorders [61]. The use of dried grapes (also called manakka) as a cardiotonic is well documented. High-performance liquid chromatography analysis of darakchasava revealed the presence of polyphenols, such as resveratrol and pterostilbene. Interest in this age-old formulation grew in light of this recent knowledge of resveratrol.

Resveratrol, *trans*-3,5,4′-trihydroxystibene, was first isolated in 1940 as a constituent of the roots of white hellebore (*Veratrum grandiflorum O. Loes*), but has since been found in various plants, including grapes, berries and peanuts [62-65]. Besides cardioprotective effects, resveratrol exhibits anticancer properties, as suggested by its ability to suppress proliferation of a wide variety of tumour cells, including lymphoid and myeloid cancers, multiple myeloma, cancers of the breast, prostate, stomach, colon, pancreas and thyroid, melanoma, head and neck squamous cell carcinomas, ovarian carcinoma, and cervical carcinoma. The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; upregulation of $p21^{Cip1/WAF1}$, p53 and Bax, downregulation of survivin, cyclin D1, cyclin E, bcl-2, bcl-X_L and cIAPs, and activation of caspases. Resveratrol has been shown to suppress the activation of several transcription factors, including NF-κB, AP-1 and Egr-1; inhibit protein kinases, including IκBα kinase, JNK, MAPK, Akt, PKC, PKD and casein kinase II; and downregulate products of genes such as COX-2, 5-lipoxygenase (5-LOX), VEGF, IL-1, IL-6, IL-8, androgen receptor and prostate-specific antigen. These activities account for this stilbene's suppression of angiogenesis. Resveratrol also has been shown to potentiate the apoptotic effects of cytokines (such as TRAIL, chemotherapeutic agents and γ-radiation. Pharmacokinetic studies have revealed that resveratrol's target organs are liver and kidney, where it is concentrated after absorption and is mainly converted to a sulfated form and a glucuronide conjugate. *In vivo*, resveratrol blocks the multistep process of carcinogenesis at various stages: It blocks carcinogen activation by inhibiting aryl hydrocarbon-induced CYP1A1 expression and activity and suppresses tumour initiation, promotion and progression. Besides chemopreventive effects, resveratrol appears to exhibit therapeutic effects against cancer. Limited data in humans have revealed that resveratrol is pharmacologically quite safe. Currently, structural analogues of resveratrol with improved bioavailability are being pursued as potential therapeutic agents for cancer.

4.4 Flavopiridol (*Dysoxylum binectariferum*)

Flavopiridol is a semisynthetic flavonoid closely related to a compound originally isolated from the stem bark of *Dysoxylum binectariferum* (also called rohitukine from *Amoora rohituka*), a plant indigenous to India and described in Ayurveda. The parent compound is identical to flavopiridol except that a methyl group replaces the chlorophenyl moiety at position 2. Flavopiridol has been shown to be a potent inhibitor of cyclin-dependent kinase (CDK) 1, CDK 2, CDK 4 and CDK 7 [66]. It inhibits CDKs by competing with adenosine triphosphate at the nucleotide-binding site on CDKs as indicated by kinetics studies [67] and X-ray crystallography of the CDK 2–flavopiridol complex [68]. The tyrosine phosphorylation of CDK 2 is also inhibited by this flavone[69]. Through inhibition of CDKs, flavopiridol induces arrest of cell growth at the G_1 and G_2 phases of the cell cycle [66,70]. Because of its ability to suppress the growth of breast carcinoma [66], lung carcinoma [71], chronic B cell leukaemia and lymphoma [72-74], multiple myeloma [75] and head and neck squamous cell carcinoma [76], flavopiridol is currently in clinical trials for the treatment of several cancers [77-79]. Flavopiridol also has been shown to enhance the activity of other growth-suppressing agents, such as TNF, doxorubicin and etoposide [80-84].

Flavopiridol also inhibits CDKs, induces apoptosis, suppresses inflammation and modulates the immune response. Flavopiridol suppressed TNF activation of NF-κB in a dose- and time-dependent manner in several cell types, with optimal inhibition occurring when cells were treated with 100 nM of flavopiridol for 6 h [85].

4.5 Zerumbone (*Zingiber zerumbet* Smith)

Zerumbone (2,6,9,9-tetramethyl-[2*E*,6*E*,10*E*]-cycloundeca-2,6,10-trien-1-one) was first isolated in 1956 from the essential oil of the rhizomes of a wild ginger, *Zingiber zerumbet* Smith, which is widespread in Southeast Asia [86,87]. Over the

years, a wide variety of activities have been ascribed to this compound [88-94]. For instance, zerumbone has been found to suppress the proliferation of colon cancer [93,94] and breast cancer [93], with minimal effects on normal cells [94]. Zerumbone also has been shown to suppress inflammation [92], suppress the initiation and promotion of skin tumours in mice [91] and prevent azoxymethane-induced aberrant crypt foci formation in rats [90]. In addition, this terpenoid has been shown to suppress dextran sodium sulphate-induced colitis in mice [95] and to inhibit the activation of the phorbol ester-induced Epstein-Barr virus [88]. Zerumbone also has been found to suppress superoxide and nitric oxide generation [89] and downregulate COX-2 [96], IL-1β [95] and TNF [94,95]. A potential explanation for several of these activities is that zerumbone may downregulate NF-κB activation [97]. The authors' laboratory has shown that zerumbone suppressed NF-κB activation induced by a variety of agents. Interestingly, α-humulene, a structural analogue of zerumbone lacking the carbonyl group, was completely inactive. Besides being inducible, constitutively active NF-κB also was inhibited. This downregulation potentiated apoptosis induced by cytokines and chemotherapeutic agents. Zerumbone's inhibition of the expression of these NF-κB-regulated genes also correlated with the suppression of TNF-induced invasion activity. Overall, this inhibition may provide a molecular basis for exploring zerumbone's potential in the prevention and treatment of cancer.

4.6 Withanolide (Withania sominifera)

The medicinal plant *Withania somnifera* is widely known for its anti-inflammatory, cardioactive and CNS effects. In Ayurveda, withanolide, which are extracted from *W. somnifera*, are employed in the treatment of arthritis and menstrual disorders and are known to be potent inhibitors of angiogenesis, inflammation, tumour development, metastasis and oxidative stress, and a promoter of cardioprotection. Many pharmacological studies have investigated the properties of *W. sominifera* in an attempt to authenticate its use as a multipurpose medical agent. Experimental studies have shown that *W. sominifera* possesses anti-inflammatory, antitumour, cardioprotective and antioxidant properties. Withaferin A, one of the compounds in the withanolide family, is a potent inhibitor of angiogenesis. It also appears to exert a positive influence on the endocrine, urogenital and central nervous systems. In recent years, herbal formulations containing substantial amounts of *W. sominifera* root extract have been evaluated in small clinical trials and shown to have efficacy in the treatment of osteoarthritis. Extracts are also known to significantly inhibit tumour growth *in vivo*. However, the mechanisms responsible for the antitumour effects of withanolide are still unknown.

The authors found that withanolide suppressed NF-κB activation induced by a wide variety of inflammatory and carcinogenic agents, including TNF, IL-1β, doxorubicin and cigarette smoke condensate. Withanolide also enhanced the apoptosis induced by TNF and chemotherapeutic agents and suppressed invasion. These results indicate that withanolide inhibit activation of NF-κB and NF-κB-regulated gene expression. This may explain their ability to enhance apoptosis and inhibit invasion.

4.7 Boswellic acid (*Boswellia serrata*)

Boswellic acid (BA) is an active component of *Boswellia serrata* (also known as Salai guggul). The gum-resin of this plant is used in Ayurvedic medicine to treat rheumatic diseases, respiratory diseases and liver disorders [98-100]. Extensive research within the last 30 years has identified the active component of this resin as BA (a pentacyclic triterpenic acid) and its derivatives (acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid [AKBA]) [101,102].

The traditional therapeutic usefulness of BA is a result of its anti-inflammatory activity, possibly mediated through the inhibition of 5-LOX [102-104] and leukocyte elastase [105,106]. In animal models of inflammation, BA has been shown to be effective against Crohn's disease, ulcerative colitis and ileitis [107-109]; adjuvant or BSA-induced arthritis [110,111]; galactosamine/endotoxin-induced hepatitis in mice [112]; and osteoarthritis [113]. BA has antitumour effects in addition to its anti-inflammatory effects. It has been found to have activity against brain tumours [114,115], leukaemic cells [116,117], colon cancer cells [118], metastatic melanoma and fibrosarcoma cells [119], and hepatoma [118]. BA also has been shown to inhibit azoxymethane-induced formation of aberrant crypt foci in the colon of mice [120].

AKBA, a component of *Boswellia serrata*, is a pentacyclic terpenoid that is active against numerous inflammatory diseases, including cancer, arthritis, chronic colitis, ulcerative colitis, Crohn's disease and bronchial asthma. The authors found that AKBA potentiates the apoptosis induced by TNF and chemotherapeutic agents, suppresses TNF-induced invasion and inhibits the receptor activator of NF-κB ligand-induced osteoclastogenesis, all of which are known to require NF-κB activation (Takada *et al.*, unpublished observations, 2005).

4.8 Fruits and vegetables

Fruits and vegetables are an integral part of Ayurvedic medicine. Steinmetz and Potter reviewed the scientific literature on the relationship between vegetable and fruit consumption and the risk of cancer [121]. After reviewing results from 206 human epidemiological studies and 22 animal studies, they found clear evidence that a higher intake of vegetables and fruits protects against cancers of the stomach, oesophagus, lung, oral cavity and pharynx, endometrium, pancreas and colon. The types of vegetables and fruits that most often appear to be protective against cancer are raw vegetables, followed by cooked allium vegetables, carrots, green vegetables, cruciferous vegetables and tomatoes. The substances in vegetables and fruits that may help protect against cancer include dithiolthiones, isothiocyanates, indole-3-carbinol (I3C),

allium compounds, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, vitamin C, d-limonene, lutein, folic acid, β-carotene, lycopene, selenium, vitamin E and dietary fibre.

How fruits and vegetables mediate their effects is beginning to be revealed [122,123]. For instance, I3C is produced by members of the family Cruciferae, and particularly members of the genus *Brassica* (for example, cabbage, radishes, cauliflower, broccoli, Brussels sprouts and daikon). Under acidic conditions, I3C is converted to a series of oligomeric products (among which 3,3'-diindolylmethane is a major component) believed to be responsible for its biological effects *in vivo*. *In vitro*, I3C has been shown to suppress the proliferation of various tumour cells, including those from breast, prostate, endometrial, and colon cancers and leukaemia; induce G_1/S cell-cycle arrest; and induce apoptosis. The cell-cycle arrest involves downregulation of cyclin D1, cyclin E, CDK2, CDK4 and CDK6 and upregulation of p15, p21 and p27. Apoptosis by I3C involves downregulation of antiapoptotic gene products, including bcl-2, bcl-X_L, survivin, IAP, X-linked inhibitor of apoptosis, and Fas-associated death domain protein-like IL-1-β-converting enzyme inhibitory protein (FLIP), upregulation of proapoptotic protein bax, release of mitochondrial cytochrome c; and activation of caspase-9 and caspase-3. This agent inhibits the activation of various transcription factors, including NF-κB, SP1, oestrogen receptor, androgen receptor and nuclear factor-E2-related factor 2. This indole potentiates the effects of TRAIL through induction of death receptors and synergises with chemotherapeutic agents through downregulation of P-gp. *In vivo*, I3C was found to be a potent chemopreventive agent for hormone-dependent cancers, such as breast and cervical cancers. These effects are mediated through its ability to induce apoptosis, inhibit DNA-carcinogen adduct formation, suppress free radical production, stimulate 2-hydroxylation of estradiol, and inhibit invasion and angiogenesis. Numerous studies have indicated that I3C also has strong hepatoprotective activity against various carcinogens. Initial clinical trials in women have shown that I3C is a promising agent against breast and cervical cancers.

5. Ayurvedic agents as chemosensitisers and radiosensitisers

Resistance of tumours to radiation and chemotherapeutic agents is common but no drug has yet been approved to overcome this chemoresistance or radioresistance. Although hydroxyurea, 5-fluorouracil and cisplatin are currently used for radiosensitisation, they are highly toxic. Recent reports point out that the safe and non-toxic agents described in Ayurvedic medicine can function as sensitisers, augmenting the effectiveness of cancer chemotherapy and radiotherapy [124]. For instance, plumbagin, derived from the plant *Plumbago zeylanica*, has been reported to enhance the effect of radiation in mice bearing sarcoma S180 and Ehrlich ascites carcinoma [125]. Tetrandrine (from root of *Stephenia tetrandra*), withaferin-A (from *Withania somnifera*), echitamine chloride (from stem bark of *Astonia scholaris*), rohitukine (from *Amoora rohituka*); curcumin (from *Curcuma longa*), and perillyl alcohol and berberine (from *Tinospora cordifolia*) have been shown to possess radiosensitising activities *in vitro* and *in vivo* [126-135]. This sensitisation is believed to occur at various levels. First, by directly competing with the ATP binding site of the multi-drug resistance (MDR) or multi-drug resistance associated protein (MRP) drug efflux pumps, curcumin can inhibit the pump and increase intracellular concentrations of chemotherapeutic drugs, such as vinblastine or vincristine. Second, by functioning as efflux substrates for pumps, such as MDR or MRP, chemopreventive agents such as genistein and green tea components ((-)-epigallocatechin-3-gallate [EGCG]) can saturate and hence titrate out the pumps, increasing the amount of chemotherapeutic drug within the cell. This type of competition with the MDR or MRP substrates in effect sensitises the cancer cell for a better cell kill by chemotherapeutic agents. Third, curcumin can interfere with the functioning of pumps such as MRP, that require a steady supply of reduced glutathione GSH because it is a known inhibitor of GSH synthetase. This type of inhibition might enhance the sensitivity of cancer cells that overexpress MRP to chemotherapeutic agents such as vincristine, arsenicals and platinum derivatives by impairing their efflux [136].

Another clinical strategy that is currently being pursued is that of targeting c-JUN expression to reduce intracellular GSH levels. Stable increases in c-JUN expression are associated with an AP-1–mediated increase in GSH synthetase levels [137]. Because curcumin targets the same elements, it would be a strong inhibitor, reducing intracellular GSH at the transcriptional level [138]. Expression of glutathione S-transferase Pi (GST-Pi) also is associated with cancer cells' resistance to chemotherapeutic agents. In a recent study, curcumin efficiently inhibited the TNF- and phorbol ester-induced AP-1 and NF-κB transcription factor binding to the sites located on the GST-Pi gene promoter in K562 leukaemia cells [138]. This process efficiently reduced GST-Pi levels, interfering with drug resistance and ultimately with apoptosis. Chemopreventive agents such as curcumin also can sensitise cancer cells to other traditional chemotherapeutic agents such as etoposide and camptothecin in another capacity. Topo-II poisons stabilise the cleavable complexes, an intermediate product of the TopoII-catalysed reaction. Accumulation of these cleavable complexes is believed to lead to cell death. Conversely, a decrease in the number of cleavable complexes could confer drug resistance.

Proteasome inhibition was recently found to decrease this inducible resistance by inhibiting the Topo-II depletion by hypoxia or glucose starvation. Moreover, the observation that proteasomal inhibitors, such as lactacystin, significantly enhance the antitumour activity of etoposide in xenografts *in vivo* strongly suggests that the Topo-II depletion occurs through a proteasomal mechanism [139]. Following this rationale, several proteasomal inhibitors, such as PS-341, are currently showing promise in Phase II clinical trials. It is worth

noting that curcumin has recently been shown to inhibit cellular proteasome activity in a concentration-dependent manner with a parallel increase in the accumulation of ubiquitinated proteins. This agent may be able to inhibit the proteasomes by inhibiting ubiquitin isopeptidase activity, as shown in recent studies [140]. Curcumin's proteasome-mediated sensitisation of cancer cells to drugs such as etoposide and camptothecin would be beneficial in the treatment of several types of cancer. This expectation is based on proteasomes' inhibition of Topo-II degradation, which would result in more DNA cleavable complexes.

Most of the chemotherapeutic agents and γ irradiation commonly administered to cancer patients activate NF-κB. NF-κB activation can lead to resistance to apoptosis. Activation of these survival processes occurs in parallel with induction of apoptosis through the same agents' activation of several caspases. In this respect, co-administration of chemopreventive agents such as curcumin would activate apoptotic pathways while downregulating cell survival pathways mediated by phosphoinositol-3 kinase and Akt proteins. This generally can be accomplished without activating the antiapoptotic pathways that, in effect, alter the bcl-2: bax ratio and contribute to the sensitising effect. The sensitising or potentiating effects of these chemopreventives would then allow cancer treatments to achieve a better target cell kill than what can be achieved by chemotherapy or radiotherapy alone. Other mechanisms by which curcumin and other chemopreventive agents may enhance the cytotoxicity of chemo- and radiotherapies include the induction of $p21^{WAF\text{-}1/CIP1}$. Recently, resveratrol was found to mediate chemosensitisation through downregulation of survivin, a cell survival gene [141]. Similarly, curcumin was found to induce radiosensitisation of prostate cancer cells through suppression of NF-κB activation [128].

Study of antitumour and radiosensitising properties of *Withania somnifera* (Ashwagandha), a well known medicinal plant, have yielded encouraging results [142]. The alcoholic extract of the dried roots of the plant as well as the active component withaferin A isolated from the extract showed significant antitumour and radiosensitising effects in experimental tumours *in vivo*, without any noticeable systemic toxicity. Withaferin A gave a sensitiser enhancement ratio of 1.5 for *in vitro* cell killing of V79 Chinese hamster cells at a non-toxic concentration of ~ 2 μM. Although the mechanism of action of this compound is not known, the studies so far indicate that *W. somnifera* could prove to be a good natural source of a potent and relatively safe radiosensitiser/chemotherapeutic agent.

Similarly, the fruit pulp of *Emblica officinalis* (EO) is an important drug used in Indian systems of medicine for several diseases and as a tonic. In view of its multifarious uses, the aqueous plant extract was tested for its radioprotective properties against sublethal γ-radiation (9 Gy) in Swiss albino mice [143]. Animals were divided into two groups and irradiated with γ-radiation externally, with or without EO extract, which was given orally at different doses before irradiation. The dose of fruit pulp extract found to be most effective against radiation was 100 mg/kg b.wt. This dose increased the survival time and reduced the mortality rate of mice significantly. Furthermore, body weight loss in EO administered irradiated animals was significantly less in comparison with animals who were given radiation only. In general, these chemopreventive agents achieve significant sensitisation by overcoming therapy-induced pro-survival gene expression in several cancers.

6. Herb–drug interactions

The present interest and widespread use of herbal remedies has created the possibility of interaction between them and pharmaceutical drugs if they are used simultaneously. A wide variety of phenolic compounds and flavonoids present in spices have been tested for their effects on 5-LOX, the key enzyme involved in biosynthesis of leukotrienes [144]. All these compounds significantly inhibited the formation of lipoxygenase in a concentration-dependent manner and the combinations of spice active principles/extracts exerted synergistic effect in inhibiting 5-LOX activity.

P-gp is responsible for the systemic disposition of numerous structurally and pharmacologically unrelated lipophilic and amphipathic drugs, carcinogens, toxins and other xenobiotics in many organs, such as the intestine, liver, kidney and brain. P-gp is vulnerable to inhibition, activation, or induction by herbal constituents. Curcumin, ginsenosides, piperine, some catechins from green tea, and silymarin from milk thistle were found to be inhibitors of P-gps, whereas some catechins from green tea increased P-gpss-mediated drug transport by heterotropic allosteric mechanism, and St. John's wort induced the intestinal expression of P-gps *in vitro* and *in vivo*. Some components (e.g., bergamottin and quercetin) from grapefruit juice were reported to modulate P-gp activity. The inhibition of P-gp by herbal constituents may provide a novel approach for reversing MDR in tumour cells, whereas the stimulation of P-gp expression or activity has implication for chemoprotective enhancement by herbal medicines. Certain natural flavonols (e.g., kaempferol, quercetin and galangin) are potent stimulators of the P-gp-mediated efflux of 7,12-dimethylbenz(a)-anthracene (a carcinogen). The modulation of P-gp activity and expression by these herb constituents may result in altered absorption and bioavailability of drugs that are P-gp substrates. This is exemplified by increased oral bioavailability of phenytoin and rifampin by piperine and decreased bioavailability of indinavir, tacrolimus, cyclosporin, digoxin and fexofenadine by coadministered St. John's wort [145].

The medicinal properties of curcumin are limited because of poor bioavailability due to its rapid metabolism in the liver and intestinal wall. When curcumin was administered with piperine the bioavailability was increased by 154% in rats. On the other hand, in humans, after a dose of 2 g curcumin alone, serum levels were either undetectable or very low. Concomitant administration of piperine increased in bioavailability by 2000% [146]. The study shows that piperine enhances

the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects. EGCG, cotreatment with piperine (from black pepper), enhanced the bioavailability of EGCG in mice [147]. These studies demonstrated the modulation of bioavailablity by a second dietary component and illustrates a mechanism for interactions between dietary chemicals.

Grapefruit juice has been shown to interact with certain drugs. The co-administration of these drugs with grapefruit juice can markedly elevate drug bioavailability, and can alter pharmacokinetic and pharmacodynamic parameters of the drug. The predominant mechanism for this interaction is the inhibition of cytochrome P450 (CYP) 3A4 in the small intestine, resulting in a significant reduction of drug presystemic metabolism. An additional mechanism is the inhibition of P-gp, a transporter that carries drug from the enterocyte back to the gut lumen, resulting in a further increase in the fraction of drug absorbed. Some calcium channel antagonists, benzodiazepines, HMG-CoA reductase inhibitors and cyclosporin are the most affected drugs [148].

Bergamottin, a furocoumarin derivative from grapefruit juice, shows inhibitory effect on simvastatin metabolism [149]. Even one glass of grapefruit juice, taken daily, considerably increases the plasma concentrations of simvastatin and simvastatin acid. Grapefruit juice may, thus, increase both the cholesterol-lowering effect and the risk of adverse effects of simvastatin [150]. In another study, Lilja *et al.* have shown that when simvastatin was taken with grapefruit juice, the mean peak serum concentration of simvastatin were increased 12.0-fold, compared with control. When simvastatin was administered 24 h after ingestion of the last dose of grapefruit juice, the peak serum concentration were increased 2.4-fold compared with control. When simvastatin was given 3 days after ingestion of grapefruit juice, the peak serum concentration were increased 1.5-fold compared with control. Seven days after ingestion of grapefruit juice, no differences in the peak serum concentration of simvastatin in comparison to control were seen. The interaction potential of even high amounts of grapefruit juice with CYP3A4 substrates dissipates within 3 – 7 days after ingestion of the last dose of grapefruit juice [151].

The use of kava (*Piper methysticum Forst. F.*) has been associated with severe hepatotoxicity. This adverse effect was not previously encountered with the traditional beverage which was prepared as a water infusion in contrast to the commercial products which are extracted with organic solvents. Kavalactones, the active principles in kava, are potent inhibitors of several of the CYP 450 enzymes, suggesting a high potential for causing pharmacokinetic interactions with drugs and other herbs which are metabolised by the same CYP 450 enzymes [152]. Furthermore, some kavalactones have been shown to possess pharmacological effects, such as blockade of GABA receptors and sodium and calcium ion channels, which may lead to pharmacodynamic interactions with other substances which possess similar pharmacological proprieties.

St. John's wort (*Hypericum perforatum L.*), used extensively for the treatment of mild-to-moderate clinical depression, has long been considered safer than the conventional pharmaceutical agents. However, its ability, through its active constituents hypericin, pseudohypericin and hyperforin, to induce intestinal P-gp/MRD1 and both intestinal and hepatic CYP3A4 enzyme, could markedly reduce the distribution and disposition of their co-substrates. In addition, St. John's wort is a potent uptake inhibitor of the neurotransmitters serotonin, noradrenaline and dopamine all of which have a role in mood control. However, presently there is very little evidence to substantiate actual pharmacokinetic and/or pharmacodynamic interaction between drugs and St. John's wort [153]. Arold *et al.* also report no relevant interaction with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St John's wort extract [154]. However, coadministration of imatinib with St. John's wort may compromise imatinib's clinical efficacy [155].

Against the background of proven efficacy in mild-to-moderate depressive disorders and an excellent tolerability profile in monotherapy, there is sufficient evidence from interaction studies and case reports to suggest that St John's wort may induce the cytochrome P450 (CYP) 3A4 enzyme system and the P-gp drug transporter in a clinically relevant manner, thereby reducing efficacy of co-medications. Drugs most prominently affected and contraindicated for concomitant use with St John's wort are metabolised via both CYP3A4 and P-gp pathways, including HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors (only CYP3A4), the immunosuppressants ciclosporin and tacrolimus, and the antineoplastic agents irinotecan and imatinib mesylate. Efficacy of hormonal contraceptives may be impaired as reflected by case reports of irregular bleedings and unwanted pregnancies. The St John's wort constituent hyperforin is probably responsible for CYP3A4 induction via activation of a nuclear steroid/pregnane and xenobiotic receptor (SXR/PXR) and hypericin may be assumed to be the P-gp inducing compound, although the available evidence is less convincing. Thus, combinations of St John's wort with serotonergic agents and other antidepressants should be restricted due to potential central pharmacodynamic interactions [156].

7. Expert opinion

The biology of cancer is much better understood today than it was a few decades ago. Despite this increasing knowledge, the incidence of cancer is higher today than it was 30 years ago. Epidemiology has revealed that certain cancers are more common among people of some cultures than others. Cancers of the lung, colon, prostate and breast are very common in Western countries; they are not as prevalent in Eastern countries. Similarly, cancers of the head and neck and of the cervix are most common in India, whereas stomach cancer is most prevalent in Japan. Migration from

native to adopted country, however, exposes an individual to the same cancer risk and incidence as that of others living in the adopted country. This phenomenon suggests a minimal role for genotype and a greater role for lifestyle. These findings have prompted the US National Cancer Institute to examine the traditional concepts of lifestyle that play a role in cancer prevention. Ayurveda is an intricate system of healing that originated in India thousands of years ago. Historical evidence of Ayurveda can be found in the ancient books of wisdom known as the Vedas that were written over 6000 years ago. Ayurveda provides novel approaches to cancer prevention that are considered safe. Ayurvedic treatment of cancer involves prevention, surgical removal of tumours, herbal remedies; dietary modifications and spiritual treatments (e.g., detoxification, rejuvenation, prayer, music therapy, aroma therapy, gem therapy, sound therapy, stress relief, meditation, yoga and astrology). The current emphasis should be laid on identification of the mechanism of action of ayurvedic drugs and the prevention and treatment of cancer by combining these treatments with modern developments in medicine.

8. Conclusions

It is estimated that > 80% of the world's population cannot afford modern medicines. In addition to cost, current cancer therapies are minimally effective and exhibit toxicities that are intolerable in most cases. This review presents evidence that agents derived from plants used in Ayurvedic medicine can be used not only to prevent cancer, but also to treat cancer. Because of their pharmacological safety, these agents can be used alone or as adjuncts to current chemotherapeutic agents to enhance therapeutic effects and minimise chemotherapy-induced toxicity. Because cancer is primarily a disease of older age, finding less toxic therapies is a major priority. This review reveals that the molecular targets of chemopreventive agents are similar to those currently being used to treat cancer. Tumour cells use multiple cell survival pathways to prevail, and agents that can suppress these multiple pathways have great potential in the treatment of cancer. The evidence indicates that most of the plant-based agents used in Ayurvedic medicine do indeed suppress multiple pathways. More research is needed in order for these agents to reach their full therapeutic potential.

Table 1. Ayurvedic plants.

Abhisuka (*Pistacia vera*)	Adhaki (*Cajanus indicus*)	Agaru (*Aquillaria agallocha*) – **Aloe wood**	Agasti (*Sesbania grandiflora Pers*)
Agnimantha (*Premna integrifolia, Premna mucronata*)	Ahiphena (*Papaver somniferum*)	Ajagandha (*Thymus serpyllum*)	Ajamoda (*Trachyspermum roxburghianum*) – **Ajowan**
Akarakarabha (*Anacyclus pyrethrum*)	Aksota (*Juglans regia*) – **Walnut**	Alabu (Lagenaria arjuna)	Amalaki (*Cajanus indicus, Emblica officinalis Gaertn*)
Amaravalli (*Cuscuta lexa*) – **Cuscuta**	Amlavetasa (*Rheum spp*) – **Rhubarb root**	Amlika (*Terminalia arjuna*)	Amra (*Mangifera indica*) – **Mango**
Amrit (*Tinospora cordifolia*) – **Guduchi**	Anantamul (*Hemedesmis indicus*) – **Indian sarasaparilla**	Ankota (*Alangium salvifolium*) – **Sage-leaved alangium**	Apamarga (*Achyranthes aspera*) – **Roughchaff**
Aragvadha (*Cassia fistula*)	Ardrak (*Zingiber officinale*) – **Ginger**	Arista (*Xanthium strumarium*) – **Cocklebur**	Asana (Bijaka) (*Pterocarpus marsupium*) – **Asarai**
Ashwagandha (*Withania somnifera*) – **Winter cherry**	Adhahpuspi (*Trichodesma indicum*)	Asoka (*Saraca asoca*)	Asphota (*Vallaris solanacea*)
Asthisamhara (*Cissus qudrangularis*)	Asvattha (*Ficus religiosa*)	Atasi (*Linum usitatissimum*)	Atibala (*Abutilon indicum*) – **Indian mallow**
Atimuktaka (*Hiptage benghalensis*)	Ativisa (*Aconitum heterophyllum*) – **Aconite**	Babbula (*Acacia arabica*)	Babuna (*Anthemum nobilis*) – **Chamomile**
Badari (*Ziziphus mauritiana*) – **Indian jujube**	Bakuci (*Psoralea corylifolia*) – **Psoralea fruit**	Bakula (*Mimusops elengi*) – **Bullet-wood tree**	Bala (*Sida cordifolia*) – **Country mallon**
Bana (*Barleria strigosa*)	Bandhujiva (*Pentapetes phoenicea*) – **Noon plant**	Ban-sangli (*Crataegus oxycantha*) – **Hawthorn berries**	Bhallataka (*Semecarpus anacardium*) – **Marking nut**
Bhanga (*Cannabis sativa*) – **True hemp**	Bharngi (*Clerodendrum Serratum*)	Bhrngaraja (*Eclipta alba*)	Bhumiyamalaki (*Phyllanthus amarus, Phyllanthus urinaria*)
Bhurja (*Betula utilis*) – **Himalayan silver birch**	Bhustrna (*Hyptis suaveolens*)	Bibhitaka (*Terminalia bellirica*) – **Belleric myroblan**	Bichu (*Urtica urens*) – **Nettle**
Bilva (*Aegel marmelos*) – **Stone apple**	Bimbi (*Coccinia indica*) – **Ivy-gourd**	Bola (*Commiphora myrrha*) – **Myrrh**	Brahmi (*Bacopa monnieri*) – **Indian pennywort**
Brhati (*Solanum indicum*)	Caksusya (*Cassia tora*)	Campaka (*Michelia champaka*) – **Champak**	**Canaka** (*Cicer arietinum*)
Cancu (*Corchorus acutangulus*)	Canda (*Angelica archangelica*)	Chandan (*Santalum album*) – **Sandalwood**	Candrasura (*Lepidium sativum*) – **Water cress**
Cangeri (*Oxalis corniculate*) – **Screw pine**	Carmakasa (*Ehretia laevis*)	Catusparna (*Catuspallava*)	Cavika (*Piper chaba*)
Chananbatva (*Chenopodium abthelminiticum*) – **Wormseed**	Chandan (*Santalum album*) – **Goose foot**	Chotti elachi (*Elettaria cardomomum*)	Citraka (*Plumbago zeylanica*)
Copacini (*Smilax china*) – **Sarsaparilla**	Coraka (*Angelica glauca*) – **Angelica spp**.	Cukrika (*Rumex vesicarius*)	Dadima (*Punica granatum*) – **Pomegranate**
Dalchini (*Cinnamomum zeylanicum*) – **Cinnamon**	Danti (*Baliospermum montanum*)	Darbha (*Imperata cylindrica*)	Daruharidra (*Berberis spp.*)
Darvi (*Berberis aristata*)	Devadaru (*Cedrus deodara*) – **Cedar**	Dhanvana (*Grewia tilaefolia*) – **Coriander**	Dhanyaka (*Coriandrum sativum*) – **Cilantro**
Dharu (*Lavendla spp.*) – **Lavender**	Dhataki (*Woodfordia fruticosa*) – **Fire-flame bush**	Dhattura (*Datura metel*)	Dhava (*Anogeissus latifolia*) – **Axle wood**
Dhavala (*Lobelia inflata*) – **Lobelia**	Dhup (*Boswellia carteri*) – **Frankincenses**	Draksha (*Vitis vinifera*) – **Grapes**	Dravanti (*Croton tiglium*) – **Purging croton**
Dronapuspi (*Leucas cephalotes*)	Dugdhika (*Euphorbia thymifolia*)	Dughdapheni (*Taraxacum vulgare*) – **Dandelion**	Duralabha (*Fagonia cretica*)
Durva (*Cynodon dactylon*) – **Scutgrass**	Ela (*Elettaria cardamonum*) – **Cardamom**	Eraka (*Typha spp.*) – **Cattail**	Eranda (*Ricinus communis*) – **Castor oil**

Hind/Sanskrit name (*Latin name*) – **English name**.

Table 1. Ayurvedic plants (continued).

Erra (*Coptis teeta*) – **Golden thred**	Ervaru (*Cucumis utilissimus*)	Fanjuim (*Tusslago farfara*) – **Clotsfoot**	Farasiyun (*Marrubium vulgare*) – **Horehound**
Gadadhar (*Artemesia santonica*) – **Santonica**	Gamathi (*Mentha piperata*) – **Pepper mint**	Gambhari (*Gmelina arborea*) – **White teak**	Gandapura (*Gaultheria procumbens*) – **Wintergreen**
Gangeruki (*Grewia tenax*)	Garudi (*Cocculus hirsutus*)	Gauriphal (*Rubus spp.*) – **Red rasberry**	Gavedhuka (*Coix lachryma-jobi*)
Girikarnika (*Clitorea ternatea*) – **Clitoria**	Godhuma (*Triticum aestivum*) – **Wheat**	Gokshura (*Tribulus terrestris*) – **Small caltrops**	Guduchi (*Tinospora cordifolia*)
Guggulu (*Commiphora mukul*) – **Indian bedellium**	Gulkairo (*Althea officinalis*) – **Marshmallow**	Guma (*Leonurus cardiaca*) – **Motherwort**	Gunja (*Abrus precatorius*) – **Crab's eye**
Hamsapadi (*Adiantum lunulatum*)	Hapusha (*Juniperus spp.*) – **Juniper berries**	Harenuka (*Amomum subulatum*)	Haridra (*Curcuma longa*) – **Turmeric**
Haritaki (*Terminalia chebula*) – **Chebulic myroblan**	Hilamocika (*Enhydra fluctnands*)	**Hingu** (*Ferula asfoetida, Ferula narthex*) – **Asafoetida**	Hribera (*Valeriana hardwickii*)
Iksu (*Saccharum officinarum*)	Indhana (*Artemesia absinthium*) – **Wormwood**	Indrayan (*Citrullus colocynthis*) – **Colocynth**	Ingudi (*Balanites roxburghii*)
Ipar (*Thymus vulgarus*)	Jalakumbhi (*Pistia stratiotes*)	Jambira (*Citrus limon*) – **Lime**	Jambu (*Syzygium cumini*)
Japa (*Hibiscus rosa-sinensis*) – **Hibiscus**	Jardalu (*Prunus armerica*)	Jati (*Jasminum grandiflorum, Jsminum officinale, Forma grandiflora*) – **Jasmine**	Jatiphala (*Myristica fragrans*) – **Nutmeg**
Jaya (*Clerodendrum phlomidis*)	Jeevanti (*Leptadenia reticulata*)	Jhandu (*Tagetes erecta*) – **Marigold**	Jimuta (*Luffa echinata*)
Jingini (*Lannea grandis*)	Jiraka (*Cumin cyminum*) – **Cumin**	Jivanti (*Leptadenia reticulata*)	Jyotismati (*Celastrus paniculatus*) – **Black ipecac**
Kachur (*Curcuma zedoary*)	Kadali (*Musa paradisiaca*) – **Banana**	Kadamba (*Anthocephalus indicus*)	Kadara (*Acacia suma*)
Kakadani (*Crdiospemum halicacabum*)	Kakajangha (*Peristrophe bicalyculata*)	Kakamaci (*Solanum nigrum*) – **Black nightshade**	Kakanasa (*Asclepias curassavica*)
Kakodumbara (*Ficus hispida*)	Kalaya (*Lathyrus sativus*)	Kamala (*Nelumbo nucifera*) – **Indian lotus**	Kampillaka (*Mallotus philippinensis*) – **Indian kamala**
Kancanara (*Bauhinia variegaa*)	Kancata (*Jussiae repens*)	Kandali (*Crinum asiaticum*)	Kanguka (*Setaria italica*)
Kanaka-dattura (*Datula alba*) – **Datura**	Kankola (*Piper cubeba*) – **Cubebs**	Kantaki karanja (*Caesalpinia crista*)	Kantakri (*Solanum surattense*) – **Yellow-berried nightshade**
Kapikacchu (*Mucuna prurita*) – **Atemagupta**	Kapittha (*Feronia limonia*) – **Wood apple**	Karanja (*Prongamia pinnata*)	Karavellaka (*Momordica charantia*)
Karavira (*Nerium indicum*)	Karcura (*Curcuma zedoaria*) – **Zedaria**	Karira (*Capparis decidua*)	Karkandhu (*Ziziphus nummularia*)
Karkaru (*Cucurbita pepo*)	Karkatakashringi (*Rhus glabra*) – **Wax tree**	Karkatasrngi (*Pistacia integemrmi*) – **Crab's claw**	Karkota (*Momordica dioica*)
Karpasi (*Gossypium herbaceum*)	Karpura (*Cinnamonum camphora*) – **Camphor tree**	Kasa (*Saccharum spontaneum*) – **Thatch grass**	Kasamarda (*Cassia occidentalis*)
Kasani (*Cichorium intybus*) – **Wild chicory**	Kaseru (*Scirpus grossus*)	Kasmarya (*Gmelina arborea*)	Katabhi (*Albizzia lucida*)
Katakah (*Strychnos potatorum*) – **Cleaning nut**	**Katphala** (*Myrica esculenta*)	Katuka (*Picrorhiza kurroa*)	Katuvira (*Capsicum frutescens*) – **Caynne pepper**
Kebuka (*Costus speciosus*)	Kesaraja (*Wedelia chinensis*)	Ketaki (*Pandamus odorotissimus*) – **Fragrant screw pine**	Khadir (*Acacia catechu*) – **Catechu**
Kharjura (*Phoenix dactylifer*) – **Dates**	Kirata tikta (*Swrtia chiratata*) – **Chiretta**	Kodrava (*Paspalum scrobiculatum*) – **Kodo millet**	Kokilaksa (*Astercantha longifolia*) – **Asteracantha**

Hind/Sanskrit name (*Latin name*) – **English name**.

Table 1. Ayurvedic plants (continued).

Kosamra (*Schleichera oleosa*) – **Lac tree**	Kosataki (*Luffa acutangula*) – **Ridged gourd**	Kovidara (*Bauhinia pupurea*)	Kramuka (*Areca catechu*) – **Betel nuts**
Krsna jiraka (*Carum carvi*)	Krsna Vetra (*Tiliacora racemosa*)	Ksiri vrksa (*Laticiferous plants*)	Kulattha (*Dolichos biflorus*) – **Horse gram**
Kulatthika (*Dolichos falcatus*)	Kumari (*Aloe vera*) – **Aloe**	Kumbhika (*Careya arborea*) – **Kumbi**	Kumkum (*Crocus sativa*) – **Saffron**
Kumuda (*Nymphoea nouchali*)	Kupilu (*Strychnos nuxvomica*) – **Snake wood**	Kurlaru (*Curcubito pepo*) – **Pumpkin seed**	Kusa (*Desmostachya bipinnata*)
Kushta (*Saussurea lappa*) – **Costus**	Kusmanda (*Benincasa hispida*) – **Ash gound**	Kusumba, Kusumbha (*Carthamus tinctorius*) – **Safflower**	Kutaja (*Holarrhena antidysenterica*)
Laghu Kantakari (*Solanum xanthocarpum*)	Lahuriya (*Plantago spp.*) – **Plantain**	Lakshmana (*Panax ginseng*) – **Ginseng**	Lasunghas (*Medicago sativa*) – **Alfalfa**
Lavanga (*Syzgium aromaticum*) – **Cloves**	Limpaka (*Citrus limonum*) – **Lemon**	Loni (*Portulaca oleracea*) – **Parsiane**	Madana (*Randia spinosa*)
Madhuka (*Glycyrriza glabra, Madhuca indica*) – **Madhuka**	Madhulika (*Eleusine carocana*) – **Finger millet**	Madyanti (*Lawsonia inermis*) – **Henna**	Majuphul (*Ouercus spp.*) – **Oak bark**
Mallika (*Jasminum sambac*) – **Jasmine arabian**	Mandukapani (*Centella asisatica)* – **Goto kola**	Manjistha (*Rubia cordifolia*) –**Indian madder**	Marica (*Piper nigrum*) – **Black pepper**
Masa (*Phaseolus mungo*)	Masaparni (*Teramnus labialis*)	Masura (*Lens culinaris*) – **Lentil**	Matsyaksaka (*Alternanthera sesilis*)
Mayurasikha (*Actiniopteris dichotoma*)	Meshashringi (*Gymena sylvestre*) – **Gurmar**	Methi (*Trigonella fornum-graecum*) – **Fenugreek**	Mhameda (*Poygonatum officinalis*)
Mishamitita (*Coptis spp.*) – **Coptis**	Mishreya (*Anthemum vulgaris*) – **Dill**	Morata (*Maerua arenaria*)	Mrthi (*Trigonella foenum-graecum*) – **Fenugreek**
Mudgaparni (*Phaseolus trilobus*)	Mukkopira (*Passiflora incarnata*) – **Passion flower**	Mulaka (*Raphanus sativaus*)	Murva (*Marsdenia tenacissma*)
Musata (*Cyperus rotundus*) – **Nut grass**	Nadica (*Corchorus olitorius*)	Nadihingu (*Gardenia floribunda*) – **Gardenia**	Nagabala (*Grewia hirsuta*)
Nagadamani (*Artemesia vulgaris*) – **Mugwort**	Neel (*Indigofera tinctrica*)	Nimb (*Avadiracta indica*) – **Neem**	Parnbeej (*Bergenia iigulata*)
Phudina (*Mentha arvensis*) – **Mint**	Pichu (*Prunus persica*) – **Peach seed**	Pippari (*Piper longum*) – **Long pepper**	Rasna (*Pluchea lanceolata, Alpnia officinarum*) – **Galangal**
Rasona (*Allium sativum*) – **Galic**	Rohisha (*Cymbopogon citrates*) – **Lemon grass**	Ruhituka (*Dysoxylum binectariferum*)	Rojmari (*Achillea millefolium*) – **Yarrow**
Ruraksa (*Elaeocarpus ganitrus*)	Rusmari (*Rosemarinus officinalis*) – **Rosemary**	Sadapaha (*Ruta graveolens*) – **Rue**	Saireyake (*Barleria prionitis*)
Sarai guggul (*Boswellia serrata*) – **Indian olibaum**	Sarjarasa (*Vateria indica*) – **Indian copal tree**	Sarpagandha (*Rauwolfia serpentina*) – **Serpiria**	Sathra (*Origanum vulgare*) – **Oregano**
Salvia (*Salvia officinalis*) – **Sage**	Senna (*Cassia angusdifola*) – **Alexandria senna**	Sevanti (*Chrysanthemum indicum*) – **Chysanthems**	Shaliparni (*Desmodium gangeticum*)
Shatapatra (*Rosa spp.*) – **Rose**	Shatavari (*Asparagus racemosus*) – **Asparagus**	Shriveshtaka (*Pinus spp.*) – **Chir pine**	Shveta musai (*Asparagus adscendens*)
Shyonaka (*Oroxylum indicum*)	Sitaphala (*Annona squamosa*) – **Sugar apple**	Snigdha-jira (*Plantago psyllium*) – **Psyllium**	Snuhi (*Euphorbia nerifolia*)
Sonf (*Foeniculum valgae*) – **Fennel**	Somalata (*Ephedra spp.*) – **Ephedra**	Soyabean (*Glycine max*) – **Soyabean**	Sthauneyaka (*Taxus baccata*)
Sudarsana (*Crinum latifolium*)	Svandu-narin-ga (*Citrus aurantium*) – **Orange peel**	Svarnaksiri (*Argemone mexicana*)	Sveta bala (*Sida rhomboidea*)
Svetasarisha (*Brassica alba*) – **Mustard**	Tagara (*Valeriana spp.*) – **Valerian rhizome**	Tailaparni (*Eucalyptus globulis*) – **Eucalyptus**	Tala (*Borassus flabellifer*) – **Palmyra palm**

Hind/Sanskrit name (*Latin name*) – **English name**.

Table 1. Ayurvedic plants (continued).

Talapatri (*Curculigo orchioides*)	Talisa (*Abies webbiana*)	Tambula (*Piper betle*)	Tanduliya (*Amaranthus spinosus*) – **Pricky amaranth**
Tejpatra (*Cinnamomum tamala*) – **Indian cinnamon**	Til (*Sesamum indicum*) – **Sesame**	Tilaka (*Wendlandia exerta*)	Tilaparni (*Cleome icosandra*)
Tilvaka (*Viburnum nervosum*)	Timira (*Eleusine aegyptiaca*)	Tinduka (*Diospyros peregrina*)	Tinisa (*Ougenia oojeinensis*)
Trapusa (*Cucumis sativus*) – **Cucumber**	Trayamana (*Gentiana kurroo*) – **Gentian**	Trepatra (*Trifolium paratense*) – **Red clover**	Trivrt (*Operculina turpethum*) – **Indian Jalap**
Tulsi (*Ocimum sanctum*) – **Holy basil**	Tumburu (*Zanthoxylum armatum*) – **Prickly ash**	Turuska (*Liquidamber orientalis*) – **Oriental sweet gum**	Tuvaraka (*Hydnocarpus laurifola*)
Tvak (*Cinnamomum zeylanicum*) – **Cinnamon**	Udumbara (*Ficus glomerata*)	Uma (*Linum usitatissimum*) – **Flaxseed**	Upakuncika (*Nigella sativa*) – **Small fennel**
Upana (*Asarum spp.*) – **Wild ginger**	Upodika (*Basella rubra*)	Urumana (*Prunus armeniaca*) – **Apricot**	Usira (*Vetiveria zizanoides*) – **Vetivert**
Uttamarani (*Prgularia daemia*)	Vacha (*Acorus calamus*) – **Sweet flag**	Vanakrpasi (*Thespesia lampas*)	Vanshalochan (*Bamboosa arundinacea*)
Varahikand (*Dioscorea bulbifera*)	Vasa (*Adathoda vasica*) – **Vasaka**	Vatma (*Amygdalus communis*)	Vidarikand (*Pueraria tuberosa*) – **Indian kudzu**
Visa (*Aconitum napellus*) – **Indian aconite**	Vrsciva (*Sveta punarnava*)	Yava (*Hordeum vulgare*) – **Barley**	Yavani (*Trachyspermum ammi*)
Yavasa (*Alhagi camelorum*)	Yuthika (*Jasminum auriculatum*)	Yvanala (*Zea mays*) – **Corn silk**	Zergul (*Calendula officinalis*) – **Calendula**
Zufa (*Nepeta cataria*)	Zupha (*Hyssopus officinalis*) – **Hyssop**		

Hind/Sanskrit name (*Latin name*) – **English name**.

Table 2. Chemical constituent from the plants used for various anti-inflammatory purposes.

Constituent	Species	Constituent	Species	Constituent	Species
Arbine	*Abrus precatorius*	Acbarlerin	*Barleria prionitis*	Achyranthine	*Achyranthes aspera*
Acidic polysaccharides	*Commiphora molmol, C. mukul, C. myrrha*	Acrylic acid	*Ananas comosus*	Acutangulic acid	*Barringtonia acutangula*
Allyl-isothiocyanate	*Brassica compestris, B. juncea*	**Aloe-emodin**	*Rumex crispus*	α- and γ-atlantone	*Cedrus deodara*
α-Amyrin acetate	*Artocarpus lakoocha*	α-Pinene	*Juniperus communis*	α-Solamarine	*Solanum dulcamara*
Amygdalin	*Cydonia oblonga*	**Andrographolide**	*Cydonia oblonga*	**Anethole**	*Foeniculum valgae, coriandrum sativum*
Anthocynin	*Hibiscus sabdariffa*	Apeginine-7-*O*-glucoside	*Salvia officinalis, Olea europea*	α-Peroxyachifolid	*Achillea millefolium*
Apigenin	*Gmeliana arborea, Indigofera tinctoria*	Apiin	*Apium graveolens*	Apiosylskimmin	*Gmeliana arborea*
Arabans	*Althaea officinalis*	Arabinogalactans	*Althaea officinalis*	Arborine	*Ruta graveolens*
Arborinine	*Ruta graveolens*	Arctic acid	*Arctium lappa*	Arctiin	*Arctium lappa*
Arctiol	*Arctium lappa*	Arteanuuin-B	*Artemisa annua*	Artemisinic acid	*Artemisa annua*
Artemisinin	*Artemisa annua*	Artumerone	*Curcuma domestica*	Asiaticoside	*Centella asiatica*
Atlantone	*Cedrus deodara, Curcuma domestica*	Augustine	*Crinum ambile, C. latifolium*	Authraquinone	*Cassia angustifolia*

Compounds with bold faces have been investigated for NF-κB. For references see [157-163].

Table 2. Chemical constituent from the plants used for various anti-inflammatory purposes (continued).

Constituent	Species	Constituent	Species	Constituent	Species
Azadirachtin	*Azadirachta indica*	Barlerin	*Barleria prionitis*	Barringtogenic acid	*Barringtonia acutangula*
Berberine	*Coptis teeta, Tiinospora cordifolia*	Bergaptene	*Apium graveolens*	Berginin	*Bergenia ligulata*
β-amyrin	*Acacia leucophloea, Barringtonia acutangula*	β-Sitosterol	*Barringtonia acutangula, Acacia leucophloea, Artocarpus lakoocha, Barleria prionitis, Capparis aphylla, C. deciduas, Cassia angustifolia, Corylus avellana, Ficus hispida, F. lacor, F. oppositifolia, Gmeliana arborea*	**β-Boswellic acid**	*Boswellia serrata*
β-Caryophylene	*Juniperus communis*	β-Elemene	*Juniperus communis*	Betaine	*Achyranthes aspera*
β-Myrcene	*Juniperus communis*	β-Pinene	*Juniperus communis*	β-solamargine	*Solanum surattense*
β-Solamarine	*Solanum dulcamara*	**Bisdemethoxy-curcumin**	*Curcuma longa*	Boeravine	*Boerhavia diffusa*
Bromelian	*Ananas comosus*	β-Selinene	*Apium graveolens*	Caffeic acid derivatives	*Citrullus colocynthis*
Caffeoyl	*Vitis vinifera*	Campasterol	*Ficus lacor*	Campho	*Curcuma aromatica, Salvia officinalis*
Cannavenin	*Melilotous alba, officinalis*	Cardenolides	*Digitalis purpurea*	Carnosolic acid	*Salvia officinalis*
Carpaine	*Carica papaya*	**Chlorogenic acid**	*Salvia officinalis*	Cholestral	*Ficus lacor, Helianthus anus*
Chryosphanol	*Rumex crispus*	Cineole	*Ruta graveolens, Salvia officinalis*	**Cinnamic acid**	*Liquidambar orientalis*
Citral	*Citrus limon, Cymbopogon citratus, C. martini, C. winterinus*	Citric acid	*Ananas comosus*	Citronellal	*Citrus limon, Cymbopogon martini, C. winterinus*
Citronyllyl acetate	*Citrus limon*	Coptin	*Coptis teeta*	Corilagin	*Syzygium cumini*
Coumarin	*Gmeliana arborea*	Coumarone acids	*Melilotous alba*	Courmarin scopoletin	*Aegle marmelos*
Crinamine	*Crinum ambile, C. latifolium*	Crocin	*Crocus sativus*	**Cucurbitacins**	*Citrullus colocynthis*
Curcumin	*Curcuma aromatica, C. domestica, C. longa*	Curcumol	*Curcuma aromatica, C. domestica, C. longa*	Curlone	*Curcuma domestica*
Cycloartenol	*Artocarpus lakoocha*	Cycloartenone	*Artocarpus lakoocha*	Daidzein	*Medicago sativa*
d-Camphene	*Curcuma aromatica*	d-Camphor	*Curcuma aromatica*	Dehydrofukinone	*Arctium lappa*
Demethoxy curcumin	*Curcuma longa*	Desmodin	*Desmodium gangeticum, D. heterocarpon*	Dianthrone glucoside	*Cassia angustifolia*
Dictamnin	*Ruta graveolens*	Dodecanal	*Citrus limon*	**Ellagic acid**	*Syzygium cumini, Punica granatum*

Compounds with bold faces have been investigated for NF-κB. For references see [157-163].

Table 2. Chemical constituent from the plants used for various anti-inflammatory purposes (continued).

Constituent	Species	Constituent	Species	Constituent	Species
Ellagitannins	*Juglans regia*	Echitamine chloride	*Astonia scholaris*	**Emodin**	*Aroe vera, Cassia angustifolia, Rumex crispus*
Epoxy fatty acid	*Syzygium cumini*	Fagarine	*Ruta graveolens*	Ferric oxide	*Corylus avellana*
Feruloylsuccinic acid	*Vitis vinifera*	Flavanol glycoside	*Barleria prionitis*	**Flavopiridol**	*Dysoxylum binectariferum*
Formononetin glycosides	*Medicago sativa*	Fraxidin	*Melilotous alba, M. officinalis*	Galacturonic rhamnans	*Althaea officinalis*
Gallic acid	*Bergenia ligulata*	Galloylglucose	*Juglans regia*	γ-Cadinene	*Juniperus communis*
γ-Murolen	*Juniperus communis*	Gangetnin	*Desmodium gangeticum*	Gedunin	*Azadirachta indica*
Genistein	*Medicago sativa, Glycine max*	Gentiopicroside	*Swertia chirayita*	Geraniol esters	*Pelargonium graveolens*
Geranyl acetate	*Citrus limon*	Glaberene	*Glycyrrhiza glabra*	Glaberidin	*Glycyrrhiza glabra*
Glucobrassicin	*Capparis sepiaria, C. spinosa, C. zeylanica*	Glucocappasalin	*Capparis aphylla, C. deciduas*	Glucosinolates	*Brassica compestris, B. juncea, B. oleracea, Capparis spinosa, C. sepiaria, C. zeylanica*
Glycyrrhetic acid	*Glycyrrhiza glabra*	Gossypetin	*Hibiscus sabdariffa*	Graveolin	*Ruta graveolens*
Gravilliferone	*Ruta graveolens*	**Guggulsterone**	*Commiphora mukul*	Hederagenin	*Medicago sativa*
Hentriacontanol	*Gmeliana arborea*	Herniarin	*Melilotous alba, M. officinalis, Ruta graveolens*	Hesperidin	*Citrus sps*
Hibiscus acid	*Hibiscus sabdariffa*	Hydropiperoside	*Polygonum hydropiper*	Hydroxycinamic acid ester	*Polygonum hydropiper*
Hyoscine	*Hyoscyamus muticus, H. niger*	Hyoscyamine	*Hyoscyamus muticus, H. niger*	Hyperoside	*Juglans regia, Polygonum hydropiper*
Hypoxanthin-9-L-arabinofuranoside	*Boerhavia diffusa*	Indole glucosinolates	*Capparis sepiaria, C. spinosa, C. Zeylanica*	Inulin	*Arctium lappa*
Iridoids	*Barleria prionitis*	Isocaproic acid	*Ananas comosus*	Isofuroxanthone	*Boerhavia diffusa*
Isoliquiritigenin	*Glycyrrhiza glabra*	Isoquercitrin	*Apium graveolens*	Isotoxine	*Abrus precatorius*
Juglon	*Juglans regia*	Kaempferol	*Indigofera tinctoria, Vitis vinifera*	Kukusaginine	*Ruta graveolens*
Lapodin	*Rumex crispus*	Leucocantho-cyanidine	*Phoenix dactylifera*	Leucocynidin	*Butea frondosa, B. monosperma*
Limonene	*Apium graveolens, Citrus limon, Juniperus communis*	Linalyl acetate	*Ruta graveolens, Citrus limon*	Linoleic acid	*Buchanania lanzan, B. latifolia, Helianthus annuus, Syzygium cumini*
Liquiritigenin	*Glycyrrhiza glabra*	Liridodendrin	*Boerhavia diffusa*	l-Stachydrine	*Capparis aphylla, C. deciduas, C. sepiaria, C. spinosa, C. zeylanica*
Lupeol acetate	*Artocarpus lakoocha, Ficus hispida, F. oppositifolia*	Lutein	*Medicago sativa*	**Luteolin**	*Gmeliana arborea, Indigofera tinctoria*

Compounds with bold faces have been investigated for NF-κB. For references see [157-163].

Table 2. Chemical constituent from the plants used for various anti-inflammatory purposes (continued).

Constituent	Species	Constituent	Species	Constituent	Species
Luteolin-7-glucosides	*Achillea millefolium, Olea europia, Salvia officinalis*	Lycopene	*Crocus sativus*	Malic acid	*Ananas comosus, Hibiscus sabdariffa, Vitis vinifera*
Maslinic acid	*Olea europia*	Menthol	*Ruta graveolens*	Methyl anthranylate	*Citrus limon*
Methyl n-propyl ketone	*Ananas comosus*	Mono ammonium glycyrrhizinate	*Glycyrrhiza glabra*	Myristic acid	*Syzygium cumini*
Nanigin	*Vitis vinifera, Citrus sps*	Napthalene glycosides	*Cassia angustifolia*	Neoandrographolide	*Andrographis paniculata*
Neopodin-8-glucoside	*Rumex crispus*	N-Hexacosanol	*Acacia leucophloea*	Nimbin	*Azadirachta indica*
Nimbolin	*Azadirachta indica*	Nitropropionic acid	*Astragalus hamosus*	n-Nonacosane	*Capparis aphylla, C. deciduas*
Nonanal	*Citrus limon*	Nonanone	*Ruta graveolens*	n-Pentacosane	*Capparis aphylla, C. deciduas*
n-Triacontane	*Capparis aphylla, C. deciduas*	n-Triacontanol	*Capparis aphylla, C. deciduas*	Oleanolic acid	*Liquidambar orientalis, Olea europia*
Oleic acid	*Buchanania lanzan, B. latifolia, Helianthus annuus, Syzygium cumini*	Oleolanic acid	*Liquidambar orientalis*	Oleonilic acid	*Olea europia*
Oleoropine	*Olea europia*	Oxalic acid	*Vitis vinifera*	Palmitic acid	*Buchanania lanzan, B. latifolia, Helianthus annuus, Hibiscus sabdariffa, Syzygium cumini*
Parthenolide	*Tanacetum parthenium*	p-Cumaroyl	*Vitis vinifera*	Pelargonidin-3-galactoside	*Capparis aphylla, C. deciduas*
Phenyl propane derivatives	*Brassica oleracea*	Phthalic acid	*Capparis aphylla, C. deciduas*	Phthalides	*Apium graveolens*
Picrocrocin	*Crocus sativus*	Piperidine derivatives	*Phoenix dactylifera*	Plumbagin	*Plumbago zeylamica*
p-methoxycinnamic acid	*Curcuma aromatica*	p-methyl-3 tetrahydroacetophenone	*Cedrus deodara*	Podophylotoxin	Podophyllum hexandrum
Polygodial	*Polygonum hydropiper*	Proanthocynidins	*Adiantum capillus*	Pseudocarpaine	*Carica papaya*
Ptelein	*Ruta graveolens*	Pterocarpanoids gangetin	*Desmodium gangeticum*	Punarnavaside	*Boerhavia diffusa*
Punicic acid	*Bryonopis laciniosa*	**Quercetin**	*Gmeliana arborea, Indigofera tinctoria, Melilotous alba, Melilotus officinalis, Vitis vinifera*	Quercitrin	*Juglans regia, Polygonum hydropiper, Rumex crispus*
Resveratrol	*Vitis vinifera*	Rhamnazine	*Polygonum hydropiper*	Rhamnazine bisulphatepersicarin	*Polygonum hydropiper*
Rhein	*Cassia angustifolia, Rumex crispus*	Rosmarinic acid	*Salvia officinalis*	Rutacultin	*Ruta graveolens*
Rutic acid	*Capparis sepiaria*	Rutin	*Achillea millefolium, Ruta graveolens*	Sabinene	*Juniperus communis*
Safranal	*Crocus sativus*	Saikosaponins	*Bupleurum falcatum*	Scoparone	*Aegle marmelos*

Compounds with bold faces have been investigated for NF-κB. For references see [157-163].

Table 2. Chemical constituent from the plants used for various anti-inflammatory purposes (continued).

Constituent	Species	Constituent	Species	Constituent	Species
Scopolatin	*Aegle marmelos, Melilotous alba, M. officinalis*	Scutellarein-7-neohesperidoside	*Barleria prionitis*	Sennosides	*Cassia angustifolia*
Sesquiterpenes	*Commiphora molmol, C. mukul, C. myrrha*	Sinigrin	*Brassica compestris, B. juncea*	Skimianin	*Ruta graveolens*
Soladulcidenetetraoside	*Solanum dulcamara*	Solamargine	*Solanum dulcamara, S. surattense*	Solasonine	*Solanum dulcamara, S. surattense*
Stearic acid	*Buchanania lanzan, B. latifolia*	Stigmasterol-3-β-*O*-D-glucucoside	*Barringtonia acutangula, Ficus lacor*	Styrene	*Liquidambar orientalis*
Swerchirin	*Swertia chirayita*	Swertiamarin	*Swertia chirayita*	Tangulic acid	*Barringtonia acutangula*
Tartaric acid	*Hibiscus sabdariffa*	Tetrandrin	*Stephenia tetrandra*	Thiamine	*Hibiscus sabdariffa*
Thujone	*Salvia officinalis*	Tragacanthine	*Astragalus sarcacola*	Trigonelline	*Melilotous alba, M. officinalis*
Tumerone	*Curcuma domestica*	Umbelliferone	*Aegle marmelos, Melilotous alba, M. officinalis, Ruta graveolens*	**Ursolic acid**	*Salvia officinalis*
Valerianic acid	*Ananas comosus*	Vanillin	*Ananas comosus*	Viscin	*Viscum album*
Warburganal	*Polygonum hydropiper*	**Withanolide**	*Withania somifera*	**Yakuchinone**	*Alpina oxyphylla, Semicarpus anacardium*
Zermbone	*Zingiber zerumbet*	Zingiberene	*Curcuma domestica*		

Compounds with bold faces have been investigated for NF-κB. For references see [157-163].

Table 3. Molecular targets of Ayurvedic plants.

Plant name	Uses	Molecular target
Asal rai (*Brassica oleracea*)	Rheumatism, sciatica, body massage	↓ NF-κB, ↓ cdc25, ↓ cdk1, ↓ Bcl-2, ↓ Bcl-X_L
Ashwagandha (*Withania somnifera*)	Anti-inflammatory, anti-arthritic and rheumatic conditions	↓ NF-κB
Bhallataka (*Semicarpus anacardium*)	Debility, worms, epilepsy, syphilis asthma, neuralgia	↓ NF-κB
Bhumiyaki (*Phyllanthus amarus*)	Jaundice, gonorrhoea, menstruation, diabetes, ulcers, sores, swelling, itching	↓ iNOS, ↓ COX-2, ↓ TNF-α, ↓ IL-1β, ↓ IL-10, ↓ NF-κB
Bilva (*Aegel marmelos*)	Constipation, diarrhoea, peptic ucler, ear diseases, respiratory disorders, diabetes	↓ NO
Citronella (*Cymbopogon winterinus*)	Indigestion, cramping pain	↓ Caspase-3
Citrus limon	Prevents hair loss	↓ Caspase-3
Citrus spp.		↓ COX-2

AR: Androgen receptor; BAR: Bile acid receptor; COX: Cyclooxygenase; CYP: Cytochrome p450; ERK: Extracellular-regulated kinase; Ftase: Farnesyl-protein transferase; FXR: Farnesoid X receptor; GST: Glutathione s-transferase; GST-px; Glutathione peroxidase; HO: Heme oxygenase; IAP: Inhibitor-of-apoptosis protein; ICAM: Intercellular cell adhesion molecule; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LOX: Lipoxygenase; MAP: Mitogen-activated protein; MDR: Multi-drug resistance; MMP: Matrix metalloprotease; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; Nrf: NF-E2-related factor; PGE: Prostaglandin; PKC: Protein kinase C; PKD: Protein kinase D; PSA: Prostate specific antigen; Ptdlns: Phosphatidylinositol; STAT: Signal transducer and activator of transcription; TF: Tissue factor; TNF: Tumour necrosis factor; VEGF: Vascular endothelial growth factor; XOD: Xanthine oxidase.*Indicates phosphorylation.

Table 3. Molecular targets of Ayurvedic plants (continued).

Plant name	Uses	Molecular target
Cukrika (*Rumex crispus*)	Constipation	↓ MMP-9, ↓ PTK, ↓ HER/neu, ↓ PI3K-cdc42/Rac1, ↑ CYP1A1, ↑ CYP1B1, ↓ NF-κB, ↓ AP-1 . ↓ MEK/ERK
Cymbopogon martini	Indigestion, cramping pain	↓ Caspase-3
Cydonia oblonga	Digestive disorders, cough, gastrointestinal catarrah, joint inflammation, injury of nipples	↓ IFN-γ, ↓ IL-2, ↓ ERK1/2, ↓ AKT*, ↓ NF-κB, ↓ NO, ↓ iNOS
Dadima (*Punica granatum*)	Cough, digestive disorders, piles, pimples, dysentery	↓ NF-κB
Dalchini (*Cinnamomun zelanicum*)	Colds, diarrhea, oedema, flu, liver problems, menorrhagia, menstrual pain, indigestion	↓ PGE_2
Dhanyaka (*Coriabdrum sativum*)	Menstrual disorders, skin diseases, conjunctivitis	↓ NF-κB ↓ AP-1 ↓ JNK ↓ MAPK
Draksha (*Vitis vinifera*)	Constipation, blood circulation, cancer	↓ COX-2, ↓ iNOS, ↓ JNK, ↓ MEK, ↓ AP-1, ↓ NF-κB, ↑ P21 $^{Cip1/WAF1}$, ↑ P53, ↑ Bax, ↑ caspases, ↓ survivin, ↓ cyclin D1, ↓ cyclin E ↓ Bcl-2, ↓ Bcl-xL, ↓ cIAP, ↓ Egr-1, ↓ PKC, ↓ PKD, ↓ casein kinase II, ↓ 5-LOX, ↓ VEGF, ↓ IL-1, ↓ IL-6, ↓ IL-8, ↓ AR, ↓ PSA, ↓ CYP1A1, ↓ TypeII-Ptdlns-4kinase, ↓ Cdc2-tyr15*, ↑ HO-1, ↑ Nrf2, ↓ endothelin-1
Erra (*Coptis teeta*)	Skin diseases, cancer	↓ COX-2, ↓ AP-1
Gambhari (*Gmeliana arborea*)	Facial paralysis, diarrhoea, bilious fever, haemoptysis, asthma, bone fracture	↓ COX-2, ↓ Akt, ↓ VEGF, ↓ HIF-1, ↓ p21/WAF1, ↓ NOS-2, ↓ MMP-9, ↓ cyclin D1, ↓ Bcl-2, ↓ IL-4, ↓ IL-13, ↓ cdc2, ↓ NF-κB
Gandhatrana (*Cymbopogon citraus*)	Insomnia	↓ Caspase-3
Gokshura (*Tribulus terrestris*)	Bladder disorders, uterine complaints, constipation, anorexia, dyspepsia, jaundice	↓ COX-2, ↓ iNOS
Guduchi (*Tinospora cordifolia*)	Asthma, rheumatism	↓ COX-2, ↓ AP-1
Guggul (*Commiphora mukul*)	Slimming aid, obesity	↓ NF-κB, ↓ IAP1, ↓ XIAP, ↓ Bfl-1/A1, ↓ Bcl-2, ↓ cFLIP, ↓ survivin ↓ cyclin D1, ↓ c-Myc, ↓ MMP-9, ↓ COX-2, ↓ VEGF, ↓ BAR, ↓ CYP7A1, ↓ FXR, ↑ CYP3A, ↓ Cyp2b10
Hapusha (*Juniperus communis*)	Dropsy, skin diseases	↓ NF-κB
Indrayan (*Citrullus colocynthis*)	Constipation, dropsy, fever	↓ NF-κB, ↓ NO,↓ STAT3
Jambulan (*Syzygium cumini*)	Diarrhoea, inflammation of the mouth, pharynx and skin	↓ NF-κB
Kachur (*Curcuma zedoary*)	Heartburn, bloating, nausea, gas, cramps and stomach pain, nervous diseases	↓ TNF-α ↓ IL-4, ↓ PGE_2 , ↓ NO
Kushta (*Saussurea lappa*)	Asthma, diuretic, antiseptic, cough, cholera, aphrodisiac, antihelmintic	↓ JNK, ↓ ERK1/2, ↓ P38 kinase, ↓ AP-1, ↓ TNF-α, ↓ NO, ↓ NF-κB, ↓ IL-1β, ↓ IL-8
Kumari (*Aloe vera*)	Acne, wound, burns, eczema	↓ NF-κB, ↑ HER-2/neu, ↑ Caspase-3, ↓ AR, ↓ MMP-9, ↑ CYP1A1, ↑ CYP1B1
Lasunghas (*Medicago sativa*)	Dropsy, heart diseases, respiratory disorders, stomachic, arthritis, hair care, hypertension	↓ IL-4, ↓ PART-1

AR: Androgen receptor; BAR: Bile acid receptor; COX: Cyclooxygenase; CYP: Cytochrome p450; ERK: Extracellular-regulated kinase; Ftase: Farnesyl-protein transferase; FXR: Farnesoid X receptor; GST: Glutathione s-transferase; GST-px; Glutathione peroxidase; HO: Heme oxygenase; IAP: Inhibitor-of-apoptosis protein; ICAM: Intercellular cell adhesion molecule; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LOX: Lipoxygenase; MAP: Mitogen-activated protein; MDR: Multi-drug resistance; MMP: Matrix metalloprotease; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; Nrf: NF-E2-related factor; PGE: Prostaglandin; PKC: Protein kinase C; PKD: Protein kinase D; PSA: Prostate specific antigen; Ptdlns: Phosphatidylinositol; STAT: Signal transducer and activator of transcription; TF: Tissue factor; TNF: Tumour necrosis factor; VEGF: Vascular endothelial growth factor; XOD: Xanthine oxidase.*Indicates phosphorylation.

Table 3. Molecular targets of Ayurvedic plants (continued).

Plant name	Uses	Molecular target
Liquidambar orientalis	Cough, bronchitis, wound, ulcers	↓ CYP
Mulethi (*Glycyrrhiza glabra*)	Constipation, muscular pains, mouth ulcers, baldness, corns, sore throat, natural sweetener and flavoring	↑ p21 CIP1/WAF1
Mustard Brassica compestris	Eczema, intestinal catarrah, colic pain, indigestion, flatulence, rhinitis, coryza, hemicrania	↓ NF-κB, ↓ cdc25, ↓ cdk1, ↓ Bcl-2, ↓ Bcl-xL
Neel (*Indigofera tinctria*)	Epilepsy, nervous diseases, bronchitis, haemorrhage, old ulcers, premature graying of hair	↓ COX-2, ↓ Akt, ↓ VEGF, ↓ HIF-1, ↓ p21/WAF1, ↓ NOS-2, ↓ MMP-9, ↓ cyclin D1, ↓ Bcl-2, ↓ IL-4, ↓ IL-13, ↓ cdc2, ↓ NF-κB,↓ STAT3
Orea europia	Dermatological preparation, diuretic for hypertonia	↓ CYP
Parnbeej (*Bergenia ligulata*)	Kidney stones, bladder stones, respiratory diseases	↓ NF-κB
Rohitukine (*Dysoxylum binectrariferum*)	Inflammation, cancer	↓ NF-κB, ↓ COX-2, ↓ cyclin D1, ↓ MMP-9
Salai guggul (*Boswellia serrata*)	Arthritis, infection and irritation in the digestive tract, obesity	↓ NF-κB, ↑ p42 MAPK, ↑ p38 MAPK, ↓ 5-LOX
Salvia (*Salvia officinalis*)	Stress, infections, graying hair, sore throat	↓ NF-κB, ↓ COX-2, ↓ MMP-9, ↓ cyclin D1, ↓ AP-1, ↓ Bcr-Ab1TK
Saunf (*Foeniculum vulgare*)	Hookworm	↓ NF-κB,↓ AP-1,↓ JNK,↓ MAPK
Senna (*Cassia angustifolia*)	Anticancer, cathartic	↓ NF-κB, ↓ AP-1, ↓ MEK/ERK
Shyonaka (*Oroxylum indicum*)	Snake bite, urinary disorder, epilepsy, indigestion	↓ O_2(-), ↓ NO
Soyabean (*Glycine max*)	Malnutrition, allergies, diabetes, dandruff, hair growth	↓ NF-κB
Tanacetum parthenium	Migraine, rheumatoid arthritis	↓ NF-κB
Tulsi (*Ocimum sanctum*)	Anti-inflammatory, expectorant, analgesic, antitumour, antibacterial	↓ NF-κB
Turmeric (*Curcuma longa*)	Antiseptic, anti-inflammatory, antioxidant	↓ NF-κB, ↓ AP-1, ↓ Egr-1, ↓ STAT1, ↓ STAT3, ↓ STAT5, ↑ PPARg, ↓ EpRE, ↓ CBP, ↓ β-catenin, ↑ Nrf2,↑ IKK, ↓ EGFR, ↓ HER2, ↓ AKt, ↓ Src, ↓ JAK2, ↓ TYK2, ↓ JNK, ↓ PKA, ↓ PKC, ↓ VCAM-1, ↓ Bcl-2, ↓ Bcl-XL, ↓ ICAM-1, ↓ TF, ↓ AR/ARP, ↓ P53, ↑ MDR, ↓ ELAM-1, ↓ FTPase, ↑ GST, ↑ GSH-px, ↓ uPA, ↑ HO, ↓ XOD, ↓ cyclin D1, ↓ 5-LOX, ↓ COX-2, ↓I NOS, ↓ MMP-9, ↓ TNF, ↓ IL-6, ↓ IL-8, ↓ IL-12
Vajradanti (*Barleria prionitis*)	Strengthens teeth, toothache, arthritis, gout, skin diseases	↓ AP-1
Zerumbone (*Zingiber zerumbet*)	Inflammation, cancer	↓ NF-κB, ↓ IAP1, ↓ XIAP, ↓ Bfl-1/A1, ↓ Bcl-2, ↓ cFLIP, ↓ survivin, ↓ cyclin D1, ↓ c-Myc, ↓ MMP-9, ↓ COX-2, ↓ TRAF1

AR: Androgen receptor; BAR: Bile acid receptor; COX: Cyclooxygenase; CYP: Cytochrome p450; ERK: Extracellular-regulated kinase; Ftase: Farnesyl-protein transferase; FXR: Farnesoid X receptor; GST: Glutathione s-transferase; GST-px; Glutathione peroxidase; HO: Heme oxygenase; IAP: Inhibitor-of-apoptosis protein; ICAM: Intercellular cell adhesion molecule; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LOX: Lipoxygenase; MAP: Mitogen-activated protein; MDR: Multi-drug resistance; MMP: Matrix metalloprotease; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; Nrf: NF-E2-related factor; PGE: Prostaglandin; PKC: Protein kinase C; PKD: Protein kinase D; PSA: Prostate specific antigen; Ptdlns: Phosphatidylinositol; STAT: Signal transducer and activator of transcription; TF: Tissue factor; TNF: Tumour necrosis factor; VEGF: Vascular endothelial growth factor; XOD: Xanthine oxidase.*Indicates phosphorylation.

Table 4. Clinical trials with phytochemicals.

Drugs	Outcomes	Conditions
Flavopiridol	• Flavopiridol and imatinib mesylate in treating patients With haematologic cancer (Phase I).	• Adult acute lymphoblastic leukaemia; adult acute myeloid leukaemia; chronic myelogenous leukaemia
	• Flavopiridol, oxaliplatin, fluorouracil, and leucovorin in treating patients with advanced solid tumours (Phase I).	• Unspecified adult solid tumour
	• Bortezomib and flavopiridol in treating patients with recurrent or refractory indolent B-cell neoplasms (Phase I).	• Adult non-Hodgkin's lymphoma; indolent or aggressive adult non-Hodgkin's lymphoma; multiple myeloma; refractory plasma cell neoplasm
	• Depsipeptide/flavopiridol infusion for cancers of the lungs, esophagus, or pleura (Phase I).	• Carcinoma, small cell carcinoma, non-small cell lung; esophageal neoplasms; mesothelioma
	• Doxorubicin and flavopiridol in treating patients with metastatic or recurrent sarcoma that cannot be removed by surgery (Phase I).	• Gastrointestinal stromal tumour; recurrent adult soft tissue sarcoma; stage IV adult soft tissue sarcoma
	• Flavopiridol plus radiation therapy followed by gemcitabine in treating patients with locally advanced, unresectable pancreatic cancer (Phase I).	• Adenocarcinoma of the pancreas; recurrent pancreatic cancer; stage II pancreatic cancer; stage III pancreatic cancer; stage IVA pancreatic cancer
	• Flavopiridol, fludarabine and rituximab in treating patients with lymphoproliferative disorders or mantle cell lymphoma (Phase I).	• Adult non-Hodgkin's lymphoma; chronic lymphocytic leukaemia; hairy cell leukaemia
	• Flavopiridol in teating patients With previously treated chronic lymphocytic leukaemia or lymphocytic lymphoma (Phase I).	• B-cell Chronic lymphocytic lLeukaemia; refractory chronic lymphocytic leukaemia; Waldenstrom's macroglobulinemia; recurrent small lymphocytic lymphoma
	• Flavopiridol in treating patients with metastatic or unresectable refractory solid tumours or haematological malignancies (Phase I).	• Unspecified adult solid tumour
	• Flavopiridol, gemcitabine and irinotecan in treating patients with unresectable or metastatic solid tumours (Phase I).	• B-cell chronic lymphocytic leukaemia; prolymphocytic leukaemia; refractory chronic
	• Flavopiridol in treating patients with chronic lymphocytic leukaemia or prolymphocytic leukaemia, lymphocytic leukaemia (Phase II).	• Adult acute erythroid leukaemia; adult acute lymphoblastic leukaemia; adult acute monoblastic and acute monocytic leukaemia
	• Flavopiridol in treating patients with relapsed or refractory acute myeloid leukaemia, acute lymphoblastic leukaemia, or chronic myelogenous leukaemia (Phase I).	• Unspecified adult solid tumour
	• Gemcitabine and flavopiridol in treating patients with solid tumours (Phase I).	• Recurrent ovarian epithelial cancer; stage IV ovarian epithelial cancer; peritoneal cavity cancer
	• Cisplatin and flavopiridol in treating patients with advanced ovarian epithelial cancer or primary peritoneal cancer (Phase II).	• Adult acute lymphoblastic leukaemia; adult acute myeloid leukaemia; secondary
	• Flavopiridol, cytarabine and mitoxantrone in treating patients with acute leukaemia (Phase II).	• Acute myeloid leukaemia
	• Combination chemotherapy in treating patients with advanced solid tumours (Phase I).	• Unspecified adult solid tumour
	• Combination chemotherapy in treating patients with locally advanced or metastatic solid tumours (Phase I).	• Unspecified adult solid tumour

Adapted from [201]. These studies are currently recruiting patients.

Table 4. Clinical trials with phytochemicals (continued).

Drugs	Outcomes	Conditions
Curcumin	• Pharmacokinetics of curcumin in healthy volunteers.	• Healthy volunteer; female
	• Gemcitabine with curcumin for pancreatic cancer (Phase II).	• Pancreatic cancer
	• Curcumin in patients with mild to moderate Alzheimer's disease (Phase II).	• Alzheimer's disease
	• Trial of curcumin in advanced pancreatic cancer (Phase II).	• Pancreatic neoplasms; adenocarcinoma
	• Use of curcumin in the lower gastrointestinal tract in familial adenomatous polyposis patients (Phase II.)	• Familial adenomatous polyposis
	• Pilot study of curcumin with or without bioperine in patients with multiple myeloma (Phase I and II).	• Multiple myeloma
	• A pilot study of curcumin and ginkgo for treating Alzheimer's disease.	• Alzheimer's disease
	• Curcumin for the chemoprevention of colorectal cancer (Phase II).	• Adenomatous polyps
	• Curcuminoids for the treatment of chronic psoriasis vulgaris (Phase II).	• Psoriasis
	• The effects of curcuminoids on aberrant crypt foci in the human colon.	• Aberrant crypt foci
Silymarin	• Silymarin (milk thistle extract) in treating patients with acute lymphoblastic leukaemia who are receiving chemotherapy (Phase II).	• Childhood acute lymphoblastic leukaemia
	• A clinical research study designed to determine if treatment of hepatitis C with milk thistle is more effective than no treatment in Patients infected with both HIV and hepatitis C (Phase I and II).	• HIV, hepatitis C
	• Botanical/drug Interactions in HIV: glucuronidation (Phase I).	• HIV seronegativity
Resveratrol	• Resveratrol in preventing cancer in healthy participants (Phase I).	• Unspecified adult solid tumour

Adapted from [201]. These studies are currently recruiting patients.

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