Review

Magnolol: A Neolignan from the Magnolia Family for the Prevention and Treatment of Cancer

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Abstract: The past few decades have witnessed widespread research to challenge carcinogenesis; however, it remains one of the most important health concerns with the worst prognosis and diagnosis. Increasing lines of evidence clearly show that the rate of cancer incidence will increase in future and will create global havoc, designating it as an epidemic. Conventional chemotherapeutics and treatment with synthetic disciplines are often associated with adverse side effects and development of chemoresistance. Thus, discovering novel economic and patient friendly drugs that are safe and efficacious is warranted. Several natural compounds have proved their potential against this dreadful disease so far. Magnolol is a hydroxylated biphenyl isolated from the root and stem bark of Magnolia tree. Magnolol can efficiently prevent or inhibit the growth of various cancers originating from different organs such as brain, breast, cervical, colon, liver, lung, prostate, skin, etc. Considering these perspectives, the current review primarily focuses on the fascinating role of magnolol against various types of cancers, and the source and chemistry of magnolol and the molecular mechanism underlying the targets of magnolol are discussed. This review proposes magnolol as a suitable candidate that can be appropriately designed and established into a potent anti-cancer drug.

Keywords: magnolol; cancer; phytochemicals; molecular targets; chemoresistance

1. Introduction

Cancer is one of the most lethal diseases and has become a major health concern globally. According to global cancer statistics and GLOBOCAN 2012 (http://globocan.iarc.fr/Default.aspx, Int. J. Mol. Sci. 2018, 19, 2362; doi:10.3390/ijms19082362 www.mdpi.com/journal/ijms
accessed on 8 July 2018), approximately 14.1 million people are diagnosed with cancer every year and it accounts for 8.2 million deaths worldwide [1]. The significant advancements made in the past few decades for unravelling the molecular causes of cancer have led to the development of numerous treatment modalities including surgery, radiation, and chemotherapy, but the disease burden still remains a challenge [2–7]. On the other hand, these chemotherapeutic agents are also associated with adverse side effects like vomiting, hyper tension, cardiovascular diseases, renal dysfunction and bone marrow destruction along with the development of chemo-resistance, which further obscures the treatment procedures and ultimately leads to cancer progression and recurrence [8–18]. Therefore, finding a remedy with minimal side effects, cost effectiveness, easy accessibility and high efficiency is of paramount importance for the effective treatment and management of this outrageous disease.

Mother Nature is the origin of 70% of the pharmaceuticals, however, there is a need to explore this vast reserve further for identification of various novel phytochemicals and chemotherapeutic agents for better management of this disease [19–32]. These natural products display inherent anti-cancer properties which emanate from a range of phytochemicals such as alkaloids, diterpenoids, flavonoids, polyphenolic compounds and sesquiterpenes obtained from various medicinal plants, fruits and vegetables [23,27,33–37]. Besides, these herbal medicines sensitize cancers to conventional therapeutic agents by regulating various oncogenic targets such as growth factors, chemokines, inflammatory enzymes and transcription factors; averting the adverse side effects of chemotherapeutic drugs, extending survival time and boosting the quality of life in cancer patients [24,38–40].

*Magnolia officinalis*, *Magnolia obovata* and *Magnolia grandiflora* are important traditional Chinese and Japanese herbal plants which possess immense medicinal properties. Magnolia bark has been extensively used as Chinese folklore medicine and is still in use in modern clinical practices [41–45]. Magnolia trees have striking features like their alluring flowers with fragrance, and petiolate leaves containing large stipules surround the stem and later fall, leaving a distinctive scar around the node; the wood of the tree is tough, light weight and easy to work, and is sought after by craftsmen [46]. Historically, the tree was used commonly for gastrointestinal disorders, anxiety, cough, acute pain, and allergic diseases. Magnolol (MAG) is hydroxylated biphenyl isolated from the root and stem bark of Magnolia tree. MAG exhibits a huge range of biological activities such as muscle relaxant, anti-oxidative, anti-atherosclerosis, anti-inflammatory, and anti-microbial effects [47–49].

Numerous preclinical studies have established that MAG exerts its effect on different types of human cancers such as those of lung, prostate, breast, gall bladder, colon, skin and hepatocellular carcinoma [50–57]. The plausible molecular mechanisms liable for the anti-cancer potential of MAG are reduced cell proliferation or cell cytotoxicity, induction of apoptosis, accumulation of reactive oxygen species (ROS), induction of autophagy and activation/inactivation of various cellular signaling pathways [46]. Several in vitro studies have led to a handful of in vivo studies on different adult animal species which demonstrated that MAG has a good safety profile, reduced tumor growth, induced apoptosis and inhibited invasion, migration and metastasis [56,58–61]. This review summarizes the underlying molecular mechanisms responsible for the anti-cancer activity that unravels the prospective of MAG as a potent candidate that can be designed and developed into an accomplished anti-cancer drug.

2. Chemistry of Magnolol

MAG is a lignan, an organic compound found in the bark of *M. officinalis* or in *M. grandiflora* with a molecular weight of 266.34 g/mol and monoisotropic mass of 266.131 g/mol. The molecular formula of MAG is C\textsubscript{18}H\textsubscript{18}O\textsubscript{2}. The melting temperature of MAG is 101.5–102 degrees Celsius and it is soluble in water at 1.24 mg/L at 25 degrees Celsius. The spectral property shows that the maximum absorption wavelength is at 293 nm [51,62–64]. The IUPAC name of MAG is 2-(2-hydroxy-5-prop-2-enylphenyl)-4-prop-2-enylphenol and it is also commonly known as 5,5′-Diallyl-[1′-biphenyl]-2,2′-dial; 5,5′-Diallyl-2,2′-biphenyldiol; 5,5′-Diallyl-2,2′-dihydroxybiphenyl; 2,2′-Bichavicol [65]. The structure of MAG is shown in Figure 1. The content of MAG in extracts of
magnolia tree is influenced by various environmental factors such as area of origin, altitude of the cultivar, the age of the tree and the part of the plant from where it is extracted [46,66–68]. The highest content of MAG was seen in the roots of the tree at a concentration of 87–96 mg/g of extract [66,68]. In view of all the influencing factors, the concentration of MAG varies from 0.05 mg/g to 91.91 mg/g in plant extracts [68]. Various methods can be used for the extraction of MAG from the extract obtained from bark, roots and leaves. These are generally aqueous and/or organic extractions, affecting the retrieval of MAG. Therefore, supercritical extraction, maceration and sonication can be employed to optimize the extraction [69].

![Structure of magnolol.](image)

Figure 1. Structure of magnolol.

3. Biological Activities of Magnolol

Several pharmacological active compounds such as magnolol, honokiol, 4-O-methylhonokiol, obovatol and few other neolignan compounds are found in the bark of Magnolia tree. MAG is reported to possess an array of pharmacological effects including anti-oxidant [70], anti-inflammatory [71], anti-bacterial [10], anti-thrombotic or anti-platelet [72], anti-stress [73], anti-anxiety, anti-Alzheimer [74], anti-stroke [75], hypoglycemic [76], smooth muscle relaxant [77,78], weight control [79], anti-dyspeptic/prokinetic [80], anti-epileptic [81], and hepatoprotective effects [82]. Small-scale clinical studies on MAG and its interaction with gamma-aminobutyric acid-A (GABA-A) and muscarinic receptors show that it helps in decreasing the anxiety levels in patients [78,83–85]. The anti-depressant activity of MAG observed in preclinical studies is due to the alterations in serotonin turnover in the frontal cortex, nucleus accumbens and striatum [86].

MAG can easily cross the blood brain barrier [87,88] and its oral bioavailability is in the region of 10%. MAG is mainly metabolized in the liver with glucuronides as its chief metabolite. Furthermore, acute or long term, preclinical or clinical studies on intake of Magnolia-based preparations did not display any biological alterations. However, very high dosage of MAG may induce hepatotoxicity in vitro [89,90]. Therefore, MAG can be used as a new generation of anti-craving, anti-abstinence, and neuroprotective drugs, with their GABA-ergic activity as well as for the treatment of spasms, convulsions and its associated pain [91]. In the cardiovascular system, it displayed vascular relaxation, anti-atherosclerosis and anti-platelet effects. In the gastrointestinal system, it demonstrated anti-gastric ulcer, anti-esophageal obstruction, hepatoprotective and anti-diarrhea effects [92].

4. Molecular Targets of Magnolol

MAG possesses an array of molecular targets that modulate the expression of different genes involved in cancer cell survival, proliferation, invasion, metastasis, chemoresistance and cell death (Figure 2). It is a well-established fact that inhibition of apoptosis is an important strategy for cancer development [37,93–96]. Release of mitochondrial cytochrome c (cyt-c) to the cytosol is controlled by a
pro-apoptotic B-cell lymphoma protein-2 (Bcl-2) family of proteins such as Bcl-2-associated X protein (Bax), BH3 interacting-domain death agonist (Bid) and Bcl-2 homologous antagonist/killer (Bak) and by the anti-apoptotic Bcl-2 family of proteins such as Bcl-2 and B-cell lymphoma-extra large (Bcl-xL) which in turn activate the intrinsic apoptosis pathway. Furthermore, it is also known that activation of caspases play a vital role in apoptosis-mediated cancer cell death [97]. The anti-cancer activity of MAG is linked with the regulation of the caspase cascades and cleaved poly (adenosine diphosphate-ribose) polymerase (PARP) [47,98–103]. Yang et al., in the year 2003, reported that MAG increased the expression of Bad, Bcl-xL, caspases-3, -6, and -9 and c-Jun N-terminal kinases (JNK) and suppressed the expression of Bcl-xL and extracellular phosphorylated signal-regulated kinase (ERK) in human lung squamous carcinoma [98]. MAG induced apoptosis via the cyt-c/caspase-3/PARP/Apoptosis inducing factor (AIF) & phosphatase and tensin homolog (PTEN)/AKT/caspase-9/PARP pathways in CGTH W-2 thyroid carcinoma cell [101]. Furthermore, MAG also induced apoptosis by enhancing the expression of PTEN and down-regulation of AKT [101,104].

MAG also exerts it anti-cancer activity by modulating various proteins involved in the cell cycle regulation [46]. Chen et al., reported that treatment of U373 glioblastoma cells with MAG induced cell cycle arrest at the G0/G1 phase by downregulating the expression of cyclin-A and -D1, and escalating the protein levels of p21/Cip1 [105]. Additionally, treatment of COLO-205 cells with MAG ameliorates the protein expression of p21 thereby inducing cell cycle arrest by inhibiting the cyclin–cyclin dependent kinases (CDKs) system [59].

Constitutive activation of nuclear factor kappa B (NF-κB) down-regulates apoptotic gene and/or upregulates anti-apoptotic gene expression. Furthermore, it also increases the expression of the genes involved in malignant conversion and tumor promotion [8,63,106–115]. It is now well known that the primary targets of MAG are NF-κB and NF-κB regulated proteins and that MAG induces cell death and reduces cell proliferation by inhibition of NF-κB activity [116–118]. MAG prevents invasion and migration of cancer cells by reversal of epithelial-mesenchymal transition (EMT) via inhibition of NF-κB activation. MAG inhibits cancer metastasis by reducing the expression of matrix metalloproteinase-7, -9 (MMP-7, -9) and urokinase plasminogen activator (uPA) [116,119].

MAG activates autophagic cell death by suppressing the levels of phosphorylated AKT and mammalian target of rapamycin (mTOR) [52]. Furthermore, it causes lung cancer autophagy by blocking the Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/PTEN/AKT pathway [120].
An MAG derivate, Ery5 inhibited angiogenesis and induced cell death via autophagy and not apoptosis in human umbilical cord vein endothelial cells (HUVEC) and PC-3 cells. In addition, treatment with MAG and knocking down of vital autophagic protein ATG7 reversed the Ery5-mediated autophagy and inhibition of angiogenesis [121]. Regulation of all these molecular targets by MAG in different malignancies will be discussed in the next section of this review.

5. Cancer Chemopreventive and Therapeutic Properties of Magnolol

Increasing lines of evidence confirm that MAG controls survival, proliferation, invasion, angiogenesis, metastasis, and chemoresistance of various types of cancers such as bladder cancer, brain cancer, breast cancer, colon cancer, leukemia, liver cancer, lung cancer, ovarian cancer, prostate cancer and skin cancer by regulating multiple signaling pathways (Figure 3). These studies provide a considerable amount of proof that MAG has significant potential as an effective multi-targeted agent for both the prevention and treatment of several cancers and are briefly summarized below.

![Figure 3. Effect of magnolol on different molecular signaling pathways. (MAG: Magnolol; T: Inhibition/Downregulation; ↑: Activation/Upregulation; T: Inhibition/Downregulation by MAG; ↑: Activation/Upregulation by MAG).](image)

6. Effect of Magnolol in Different Cancers

6.1. Bladder Cancer

Approximately 429,800 new cases and 165,100 deaths occurred globally due to bladder cancer in 2012 [1]. Various studies have shown the efficacy of MAG against this cancer (Table 1). Treatment of MAG with the human urinary bladder cancer 5637 cells showed that it promoted apoptosis and arrested the cells at the G2/M phase of the cell cycle. This anti-cancer activity is achieved through downregulation of cyclin and CDK expression and upregulated expression of the CDK inhibitor p27Kip1 [122]. Another study conducted by the same group of scientists revealed that MAG treatment of 5637 bladder cancer cells inhibits expression of MMP-9 induced by Tumor necrosis factor–alpha (TNF-α) by decreasing the binding affinity of the transcription factor NF-κB to the MMP-9 promoter [103]. MAG attenuated angiogenesis in vitro and in vivo which is mediated by inhibition of the expression of hypoxia-inducible factors-1α (HIF-1α) and vascular endothelial growth factor (VEGF) secretion in human bladder cancer cells [123]. In an animal study on bladder cancer-bearing mice, MAG downregulated the expression of transcriptional factor Forkhead box O3
(FoxO3), ubiquitin ligase, MuRF-1 and MAFbx/atrogin-1. MAG has an anti-atrophic effect on cells undergoing chemotherapy [53].

Table 1. Magnolol (MAG) and its mechanism of actions against different cancers.

| Cancer | Models | Mechanism(s) of Action | References |
|--------|--------|-------------------------|------------|
| Bladder cancer | In vivo | ↓ Myostatin, activin A formation, FoxO3, ubiquitin ligases MuRF-1 & MAFbx/atrogen-1 | [53] |
| | In vitro | ↑ p27Kip1, ↓ cyclin-B1/CDC2 | [122] |
| | In vitro | ↑ MMP-9 | [103] |
| | In vitro | ↓ HIF-1α/VEGF-dependent angiogenesis pathways | [123] |
| | In vivo | ↓ HIF-1α/VEGF-dependent angiogenesis pathways | [123] |
| | In vitro | ↑ miR-200c & E-cadherin | [54] |
| | In vitro | ↓ LOX | [124] |
| | In vitro | ↓ MMP-9 | [103] |
| | In vitro | ↓ HIF-1α/VEGF-dependent angiogenesis pathways | [123] |
| | In vivo | ↓ HIF-1α/VEGF-dependent angiogenesis pathways | [123] |
| Breast cancer | In vitro | ↑ miR-200c & E-cadherin | [54] |
| | In vitro | ↓ LOX | [124] |
| | In vitro | ↓ MMP-9 | [103] |
| | In vitro | ↓ Cell growth | [125] |
| | In vitro | ↓ HIF-1α/VEGF-dependent angiogenesis pathways | [123] |
| Cervical cancer | In vitro | ↓ Cell survival | [127] |
| | In vitro | ↓ P-gp & MDR | [128] |
| | In vitro | ↑ Cell cytotoxicity | [129] |
| | In vitro | ↑ Cell cycle arrest at G2/M phase, ROS, release of cyt-c, Bax, p21 & p53, ↓ MMP, Bcl-2, cyclin-B1 & CDC1 | [126] |
| | In vitro | ↑ Cell cycle arrest at G2/M phase, ROS, release of cyt-c, Bax, p21 & p53, ↓ MMP, Bcl-2, cyclin-B1 & CDC1 | [126] |
| Cholangiocarcinoma | In vitro | ↑ Cell cycle arrest at G2/M phase, ROS, release of cyt-c, Bax, p21 & p53, ↓ MMP, Bcl-2, cyclin-B1 & CDC1 | [130] |
| | In vivo | ↑ Tumor growth | [130] |
| | In vitro | ↑ Cell cycle arrest at G2/M phase, ROS, release of cyt-c, Bax, p21 & p53, ↓ MMP, Bcl-2, cyclin-B1 & CDC1 | [126] |
| Colon cancer | In vitro | ↑ ERK phosphorylation, p21, ↓ thymidine incorporation | [131] |
| | In vitro | ↓ β-catenin, MMP-7, uPA & c-myc | [109] |
| | In vitro | ↓ Invasion & motility of tumor cells | [109] |
| | In vitro | ↑ p53, Bax & AMPK activation, ↓ Bcl-2 | [132] |
| | In vitro | ↑ Apoptosis & p27Cip1 protein | [133] |
| | In vitro | ↑ p27Kip1 & apoptosis | [133] |
| | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1 | [133] |
| | In vitro | ↑ p27Kip1 & apoptosis | [133] |
| | In vitro | ↑ p27Kip1 & apoptosis | [133] |
| | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1, ↓ cyclins -A & -D1 & DNA synthesis | [105] |
| | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1, ↓ cyclins -A & -D1 & DNA synthesis | [105] |
| Gastric cancer | In vitro | ↑ PI3K/AKT signaling pathways | [133] |
| | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1, ↓ cyclins -A & -D1 & DNA synthesis | [105] |
| | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1, ↓ cyclins -A & -D1 & DNA synthesis | [105] |
| Glioblastoma | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1, ↓ cyclins -A & -D1 & DNA synthesis | [105] |
| | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1, ↓ cyclins -A & -D1 & DNA synthesis | [105] |
| | In vitro | ↑ Cell cycle arrest at G0/G1 phase & p21/Cip1, ↓ cyclins -A & -D1 & DNA synthesis | [105] |
| | In vitro | ↑ Cell survival | [127] |
| Kidney cancer | In vitro | ↑ Cell survival, invasion & metastasis | [61] |
| | In vivo | ↑ Cell survival, invasion & metastasis | [61] |
| Leukemia | In vitro | ↑ Cell cycle arrest at G2/M phase, ROS, release of cyt-c, Bax, p21 & p53, ↓ MMP, Bcl-2, cyclin-B1 & CDC1 | [126] |
| | In vitro | ↑ Cell cycle arrest at G2/M phase, ROS, release of cyt-c, Bax, p21 & p53, ↓ MMP, Bcl-2, cyclin-B1 & CDC1 | [126] |
| | In vitro | ↑ Cell cycle arrest at G2/M phase, ROS, release of cyt-c, Bax, p21 & p53, ↓ MMP, Bcl-2, cyclin-B1 & CDC1 | [126] |
Table 1. Cont.

| Cancer        | Models       | Mechanism(s) of Action                                                                 | References |
|---------------|--------------|---------------------------------------------------------------------------------------|------------|
| Liver cancer  | In vitro     | ↓ Cell viability                                                                       | [51]       |
|               | In vitro     | ↓ Cell survival                                                                        | [127]      |
|               | In vitro     | ↓ Cell proliferation                                                                   | [141]      |
|               | In vitro     | ↓ Cell viability                                                                       | [142]      |
|               | In vitro     | ↑ Cytosolic free Ca (2+), translocation of cyt-c, caspase-3, -8, & -9, Bcl-2           | [57]       |
|               | In vitro     | ↑ DNA synthesis                                                                        | [59]       |
|               | In vivo      | ↓ Tumor growth                                                                         | [61]       |
|               | In vitro     | ↑ Cell cytotoxicity                                                                     | [129]      |
|               | In vitro     | ↑ Cell cytotoxicity                                                                     | [143]      |
| Lung cancer   | In vitro     | ↑ Cell cycle arrest in M phase, polymerization of microtubule, apoptosis via p33-independent pathway & autophagy via AKT/mTOR | [52]       |
|               | In vivo      | ↓ Tumor growth                                                                         | [52]       |
|               | In vitro     | ↓ Cell proliferation                                                                   | [144]      |
|               | In vitro     | ↑ Cell apoptosis cell cycle arrest in G0/G1 phase, TRAIL-R2 (DR5), Bax, caspase-3, & cleaved PARP | [145]      |
|               | In vivo      | ↓ Tumor growth                                                                         | [145]      |
|               | In vitro     | ↑ Bad, Bcl-xl, & caspase-9, -3 & -6, Bcl-xl                                            | [98]       |
|               | In vivo      | ↓ Tumor growth, invasion & metastasis                                                  | [61]       |
|               | In vitro     | ↑ NF-κB activation                                                                      | [117]      |
|               | In vitro     | ↑ Autophagy, PI3K/PTEN/AKT pathway                                                     | [120]      |
|               | In vitro     | ↑ Caspase-3 & cleavage of PARP, NF-κB/Rel A                                             | [118]      |
|               | In vitro     | ↑ Release of Bid, Bax & cyt-c from mitochondria, PI3K/AKT & ERK1/2                     | [146]      |
| Melanoma      | In vitro     | ↑ Caspase-3, -8, -9 activities                                                         | [147]      |
| Neuroblastoma | In vivo      | ↓ Cytosolic free Ca (2+), via PLC-mediated pathway                                       | [60]       |
| Oral cancer   | In vitro     | ↑ Ca (2+) influx via PKC-sensitive store-operated Ca (2+) entry & ↑ Ca (2+) release from ER in a PLC-associated manner | [148]      |
| Ovarian cancer| In vitro     | ↑ Cell cytotoxicity                                                                     | [129]      |
|               | In vitro     | ↑ P-gp                                                                                 | [150]      |
| Prostate cancer| In vitro    | ↑ IGF-1, IGFBP-5, p-IGF-1R & ↑ IGFBP-3, IGF-1R                                         | [151]      |
|               | In vitro     | ↑ Cell cytotoxicity, ↑ cyclins -A, -B1, -D1 & -E, ↑ CDK-2 & -4                          | [55]       |
|               | In vitro     | ↑ Inhibiting the EGFR/PI3K/AKT signaling, ↑ cyt-c release, Bax                        | [152]      |
|               | In vitro     | ↑ MMP-2 & MMP-9                                                                         | [153]      |
|               | In vitro     | ↑ Autophagy, ↑ cell proliferation, migration, invasion & tube formation                | [121]      |
| Skin cancer   | In vitro     | ↑ GA55 & apoptosis                                                                      | [154]      |
|               | In vivo      | ↑ Tumor growth                                                                          | [56]       |
|               | In vivo      | ↑ ERK-1/2, MAPK, PI3K/AKT, iNOS & COX-2                                               | [155]      |
|               | In vivo      | ↑ Cleavage of caspase-8 & PARP, p21 & G2/M phase cell cycle arrest                      | [156]      |
|               | In vitro     | ↑ G2/M phase cell cycle arrest, Cip/p21, cleavage of caspase-8 & PARP, ↑ cyclin-B1, -A, CDK-4, CDC2 | [156]      |
|               | In vivo      | ↑ Cell viability & proliferation & apoptosis                                           | [157]      |
|               | In vitro     | ↑ Cell proliferation, Bax & Bcl-2 & apoptosis & caspases-3, 8, 9                       | [147]      |
| Spleen cancer | In vivo      | ↑ Tumor growth, invasion & metastasis                                                  | [61]       |
| Thyroid cancer| In vitro     | ↑ Apoptosis via the cyt-c/caspase-3/PARP/AIF & PTEN/AKT/caspase-9/PARP pathways & necrosis via PARP activation | [101]      |

6.2. Brain Cancer

Glioblastoma multiforme (GBM) is the most encroaching primary malignant tumor of the central nervous system [158]. A study conducted by Chen L.C. et al., on the effect of MAG has shown it to induce anti-proliferative activity against the U373 human glioblastoma cell line. MAG downregulated the expression of cyclins A and D1 and upregulated the expression of p21/Cip1 which ultimately resulted in cell cycle arrest at the G0/G1 phase [105]. Another group of scientists showed that MAG at a higher concentration of 100 μM induced apoptosis and DNA fragmentation through upregulation of p27Kip1 protein expression in U373 cells both in vitro and in vivo [133]. Preclinical studies on the
effect of combination of MAG and honokiol in U87MG and LN229 glioma cells and the human GBM orthotopic xenograft model showed that MAG acts synergistically with honokiol and halts tumor progression by regulating cyclin-A, -D1 and CDK-2, -4, -6 and through induction of autophagy and apoptosis [136]. Furthermore, another in vitro study on LN229 and U87MG glioma cell lines revealed that MAG downregulates myosin light chain phosphatase and N-cadherin protein expression level, which plays a pivotal role in cell migration and malignancy [137]. Preclinical studies on treatment of MAG with rat cortical neurons and human neuroblastoma SH-SY5Y cells showed an increase in calcium level in cells via the phospholipase C (PLC)-mediated pathway where calcium is released into the cytoplasm from intracellular storage (Table 1) [60].

6.3. Breast Cancer
Breast cancer is the most commonly diagnosed cancer and is one of the leading causes of cancer death in women worldwide [1]. In vitro and in vivo studies on the effect of MAG against cells of the highly invasive human breast cancer cell line MDA-MB-231 and female nude immunodeficient mice revealed that MAG downregulates MMP-9 expression by inhibiting the binding of NF-κB to the MMP-9 promoter [116]. MAG causes cell cycle arrest at the G2/M phase in MCF-7 cells and induces the caspase independent intrinsic apoptotic pathway mediated by enhanced reactive oxygen species (ROS) production, upregulation of proapoptotic proteins like Bax, p21 and p53, down-regulation of anti-apoptotic proteins like Bcl-2, cyclin-B1 and CDK-1 and translocation of cyt-c and release of AIF from mitochondria to the cytosol [126]. Hou X. et al., disclosed the anti-proliferative activity of MAG by analytical techniques such as 2D LC-MS, where it was found that MAG inhibits the growth of the MDA-MB-231 cell line [125]. MAG can potentially diminish metastasis by inhibiting enzyme Lysyl oxidase (LOX) and downregulation of focal adhesion kinase expression which is considered as a strong mechanism by which extracellular matrix remodulation takes place during metastasis [124]. Hagiwara K. et al., identified that MAG treatment has the ability to induce novel tumor suppressor microRNA-200c (miRNA-200c) which led to ZEB1 inhibition and E-cadherin induction in breast cancer cells (Table 1) [54].

6.4. Colorectal Cancer
According to the global cancer statistics 2012, colorectal cancer is the third most common cancer [1]. Interestingly, MAG treatment with colon cancer induced apoptosis by upregulating the expression of the p27Cip1 protein [133]. Park J.B. et al., reported that HCT-116 colon cancer cells upon treatment with MAG activated AMP-activated protein kinase (AMPK), enhanced the expression of pro-apoptotic protein Bax and p53 and downregulated the anti-apoptotic protein Bcl-2 [132]. Another study conducted by Kang Y.J. et al., in 2012 demonstrated that MAG potentially inhibited Wnt3a-mediated β-catenin translocation into the nucleus and suppressed the expression of c-myc, MMP-7, and uPA in SW480 and HCT116 human colon cancer cells [119]. In vitro and in vivo studies showed treatment with MAG induced cell cycle arrest at the G1/G0 phase of the cell cycle by increasing the p21 level and decreasing DNA synthesis [131]. Two different studies conducted by the same group indicated that MAG induced apoptosis in COLO205 cells by downregulating the expression of Bcl-2 protein and increasing the cytosolic free Ca (2+) level, cyt-c translocation from mitochondria to cytosol and activation of caspase-3, -8 and -9 [57]. It suppressed proliferation of cells by inhibiting DNA synthesis and arrested the cells at the G0/G1 phase of the cell cycle. Furthermore, COLO-205 cells implanted subcutaneously in nude mice upon treatment with MAG led to profound regression of these tumors which was mediated by the increase in the p21 protein expression level and the induction of apoptosis (Table 1) [59].

6.5. Leukemia
Leukemia occurs in the tissue that forms blood. The incidence and the mortality rate of this cancer is increasing significantly every year. MAG treatment effectively inhibited proliferation of human
HL-60 cells and Jurkat-T leukemia cells by promoting apoptosis in a dose- and time-dependent manner which was mediated through increased cytosolic cyt-c concentration, proteolytic cleavage of PARP and activated caspase-2, -3 and -9 activities [139]. Ikai T. et al., in the year 2006 reported that MAG treatment with human leukemia U937 cells induced caspase independent apoptosis by diminishing the mitochondrial membrane potential, Bcl-2 protein expression and ERK signaling pathway [140]. In addition, it also increased the translocation of apoptosis inducing factor (AIF) from mitochondria to the cytosol [140]. MAG was found to exert its anti-cancer activities against human myeloid leukemia HL-60 cells by augmenting the level of Bax and cleavage of caspase-3 and repressing the PI3K/AKT pathway which led to the induction of apoptosis and autophagy [121]. In an in vivo study, treatment of rat basophilic leukemia (RBL)-2H3 cells with MAG showed decreased leukotriene (LT) C4 and LTB4 production. Moreover, MAG also decreased the Ca (2+) level within the cells, resulting in inhibition of two Ca (2+) dependent enzymes, i.e., cytosolic phospholipase A2 (PLA2) and 5-lipoxygenase (5-LO). It also inhibited the functioning of two other enzymes, namely, LTC4 synthase and LTA4 hydrolase which are essential for LT-synthesis (Table 1) [138].

6.6. Liver Cancer

Liver cancer accounts for second highest death from cancer globally [1,159]. Many in vitro and in vivo investigations offer evidence of the effectiveness of MAG against liver cancer where it is found to increase cell cytotoxicity, repress cell proliferation/cell viability and reduce tumor growth significantly [61,127,129,141–143]. MAG induced apoptosis in HepG2 cells by increasing the intracellular level of calcium along with increased translocation of cyt-c from mitochondria to the cytosol and activation of caspase-3, -8, and -9 [57]. Another in vitro study on the same cell line conducted by the same group displayed enhanced apoptosis by upregulation of the p21 protein and inhibition of DNA synthesis. Therefore, it arrested the cell cycle progression at the G0/G1 phase of the cell cycle [59]. Furthermore, Maioli M. et al., in 2018, reported that modifying the MAG hydroxyl group into a suitable ester derivative showed a decrease in hepatic tumor malignancy (Table 1) [51].

6.7. Lung Cancer

Lung cancer is the leading cause of death in males and has surpassed breast cancer as the leading cause of cancer death among females [1]. MAG is known to repress cell proliferation and reduce tumor growth, invasion and metastasis in lung cancer (Table 1) [61,144]. Non-small cell lung cancer cell lines (NSCLC) such as A549, H441 and H520 upon treatment with MAG increased DNA fragmentation, exhibited a change in mitochondrial membrane potential and release of pro-apoptotic proteins like Bid, Bax and cyt-c from mitochondria resulting in the induction of apoptosis. Further, it also helped in the nuclear translocation of AIF, activation of endonuclease G and cleavage of PARP (caspase independent apoptotic pathway) [146]. In vitro studies on A549 and H1299 cells showed that MAG causes cell cycle arrest at the G0/G1 phase while simultaneously upregulating pro-apoptotic proteins expression, including TRAIL-R2 (DR5), Bax, caspase-3, cleaved caspase-3, and cleaved PARP. Further, in the same study, the scientists reported that in vivo A549 xenograft model upon treatment with MAG suppressed tumor growth and induced apoptosis by epigenetically activating DR5, which in turn activated death receptor-mediated apoptosis [145]. Seo J.U. et al., in 2011, revealed that MAG can alter the cell cycle in A549 cells and can also mediate caspase-dependent apoptosis via downregulation of NF-κB/Rel A in the nucleus [118]. Another study on small lung cancer H460 cells demonstrated that MAG initiates cell death via autophagy instead of apoptosis [120]. Ahn K.S. et al., reported that MAG inhibited NF-κB activation in H1299 cells [117]. MAG treatment inhibited proliferation and induced apoptosis of CH27 cells through downregulation of the Bcl-2 family, increase in cytosolic cyt-c and activation of caspase-9, -3 and -6 [98]. In vitro studies on A549 cells confirmed that MAG causes cell cycle arrest at the mitotic phase by inhibiting microtubule polymerization, and in vivo studies on the xenograft model of human A549 NSCLC tumor showed a reduction in tumor growth and size [52].
6.8. Ovarian Cancer

Although the rate of incidence of ovarian cancer is not as high as breast cancer and lung cancer, it remains one of the leading causes of deaths due to cancer among women. MAG effectively induced cell cytotoxicity and reduced cell proliferative activity in OVCAR-3 cells [129]. MAG treated with HER2-overexpressing ovarian cancer cells showed downregulation of HER2 mRNA expression mediated by the suppression of VEGF, MMP-2, cyclin-D1 proteins and the PI3K/AKT/mTOR-signaling pathway and enhancement in PARP cleavage and activated caspase-3 [149]. It was evident from the report of Han H.K. et al., that MAG significantly reduced multidrug resistance (MDR) via the downregulation of phosphorylated-glycoprotein (P-gp) expression (Table 1) [150].

6.9. Prostate Cancer

Approximately 1.1 million new cases of prostate cancer occurred in 2012, and this is the second most frequently diagnosed cancer in men worldwide [1,160]. Several preclinical studies have shown the efficacy of MAG against prostate cancer. MAG treatment of PC-3 cells can potentially induce apoptosis by decreasing the concentration of phosphorylated AKT and the epidermal growth factor receptor (EGFR) signal transduction pathway. Further, it decreased phosphorylation of serine 136 of Bad protein, assisted in the translocation of Bax to mitochondria and promoted the release of cyt-c, which in turn activated downstream caspase cascade to induce apoptosis [152]. MAG diminishes cell proliferation activity by autophagy and inhibits angiogenesis in PC3 cells [121]. Hwang E.S. et al. reported that MAG suppressed the metastatic property of PC-3 cells via downregulation of MMP-2, -9 both at the transcriptional and translational levels [153]. In vitro studies on androgen insensitive prostate cancer cell lines DU 145 and PC3 cells disclosed that MAG treatment causes cytotoxicity and affects the cell cycle progression by arresting the cells at the G2/M phase of the cell cycle by suppressing the expression of cell cycle regulatory proteins such as cyclin-A, -B1, -D1 and -E, and kinases like CDK-2 and CDK-4 [55]. The same research team performed another preclinical study on LNCap and PC3 cells and revealed that treatment with MAG downregulated the expression of Insulin-like growth factor-1 (IGF-1) and associated proteins such as insulin-like growth factor binding Protein-5 (IGFBP-5) and IGFBP-4 (Table 1) [151].

6.10. Skin Cancer

Malignant melanoma of the skin is an important global health problem. It is the most commonly diagnosed cancer, found predominantly in the white population [161]. Various preclinical studies showed MAG to be effective against skin cancer. A study conducted by Wang T.H. et al., reported that MAG induced apoptosis by upregulating the expression of the long non-coding RNA of growth arrest-specific 5 (GAS5) [154]. Further, MAG treatment can prevent chemically and UVB-induced skin cancer by inducing apoptosis [157]. MAG inhibits the expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and nuclear translocation of the NF-κB subunit thereby reducing its efficacy to bind with DNA. Furthermore, MAG also suppressed ERK1/2 kinase, MAPK, and the PI3K/AKT pathway in DMBA/TPA-induced skin cancer in female mice [155]. MAG inhibited cell proliferation in the human malignant melanoma A375-S2 cell line by increasing caspases-3, -8,-9 activities, augmenting the expression of anti-apoptotic mitochondrial protein Bcl-2 while decreasing the expression of pro-apoptotic protein Bax [147]. In vivo studies on different animal models of skin cancer demonstrated that MAG reduced tumor growth, induced apoptosis and arrested cell cycle at the G2/M phase (Table 1) [56,156,157].

6.11. Other Cancers

As discussed above, MAG possesses a potent anti-cancer effect against different types of cancers. In addition to the above-mentioned cancers, it has been found to be effective against other cancers as well such as gall-bladder cancer, fibrosarcoma, oral cancer, thyroid cancer, cholangiocarcinoma, cervical
cancer, gastric cancer, kidney cancer and spleen cancer (Table 1). However, only a handful of literature is available on the effect of MAG in these cancers. Gallbladder cancer is a relatively rare cancer and the prevalence of this cancer shows geographical and racial variations. It is common in central and eastern Europe, central and South America, Japan and northern India [162]. MAG downregulated the expression of cyclin-D1, CDC25A, and CDK-2 protein and upregulated the expression of p53 and p21 proteins in human gallbladder cancer cell lines GBC-SD and SGC-996. Further, the in vivo study showed that MAG treatment of BALB/c homozygous nude mice reduced tumor growth significantly [58].

Fibrosarcoma, commonly known as fibroblastic sarcoma, is a malignant mesenchymal tumor which originates from fibrous connective tissue. MAG efficiently reduced malignancy in human fibrosarcoma cell line HT-1080 through inhibition of MMP-9 activity [134]. In 2012, approximately 300,400 new cases and 145,400 deaths occurred due to oral cancer globally [1]. An investigation on the efficacy of MAG against OC2 oral cancer cells showed that it increases Ca (2+) concentration within the cells via PLC dependent endoplasmic reticulum release and Ca (2+) influx via store-operated Ca (2+) channels (SOC) activated by protein kinase C (PKC) [148]. Thyroid cancer is a cancer that initiates from the tissues of the thyroid gland and gradually the rate of cancer incidence is increasing every year. It was reported by Huang et al. that MAG treatment of CGTH W-2 thyroid carcinoma cells, robustly induced apoptosis by augmenting the expression of activated caspases. Apoptosis was mediated by the cyt-c/caspase-3/PARP/AIF and PTEN/AKT/caspase-9/PARP pathways whereas necrosis induced by MAG occurred via PARP activation [101]. Gastric cancer is the fourth most commonly diagnosed cancer in the world. The effects of MAG on SGC-7901 gastric cancer cells showed that it induced morphological changes in the cells and its cytotoxic effects were associated with DNA damage, the mitochondrial-mediated apoptosis pathway, increased ratio of Bax/Bcl-2, dissipation of mitochondrial membrane potential and sequential activation of caspase-3 and inhibition of PI3K/AKT-dependent pathways [135].

Cholangiocarcinoma is a malignancy that arises primarily from the epithelial lining of the bile duct. Treatment of cholangiocarcinoma CCA cells with MAG decreased malignancy and proliferation of the cells by downregulation of PCNA, Ki67, MMP-2, -7 and -9 protein expression and inhibition of the NF-κB signaling pathway [130]. Around 265,700 deaths occurred worldwide due to cervical cancer in 2012. It is the third leading cause of cancer death among females in less developed countries [163]. Two different studies conducted by Li M. et al., and Syu W.J. et al., on Hela cells reported that MAG increased cell cytotoxicity and reduced the cell survival capability of the cancer cells [127,129]. Moreover, MAG strongly inhibited TNF-α stimulated NF-κB activation and prevented MDR in KB/MDR1 cells by decreasing P-gp expression [128]. Kidney cancer, generally known as renal cancer, is a type of cancer that originates in the cells of the kidney [164]. MAG displays potent anti-cancer activity against human renal tubular ACHN cells [127]. Spleen cancer is a very rarely occurring cancer that develops in the spleen. Ikeda K. et al., in 2003, suggested that treatment with MAG in vivo displayed a substantial reduction in tumor growth, invasion and metastasis [61].

7. Conclusions

MAG, honokiol, 4-O-methylhonokiol, obovatol and other neolignans found in the bark of Magnolia tree are some of the principle compounds that confer medicinal qualities to the plant. MAG, an organic compound (lignan) isolated from various Magnolia species, has been studied extensively for its biological activities such as anti-oxidant, anti-inflammatory, anti-bacterial, anti-thrombotic or anti-platelet, anti-stress, anti-anxiety, anti-Alzheimer, anti-stroke, hypoglycemic, smooth muscle relaxant, weight control, anti-dyspeptic/prokinetic, anti-epileptic and hepatoprotective activities. Numerous preclinical studies on MAG have shown its cytotoxic potential against different cancers and other medical conditions. Through several molecular mechanisms, MAG suppressed the pathogenesis and repressed the spread of cancer in vitro and in vivo. It acts via onset of the tumor suppressor p53
pathway and inhibition/downregulation of tumor progression NF-κB, Wnt/β-catenin, PI3K-AKT and MAPK/ERK pathways.

The molecular targets associated with MAG activity are enzymes, apoptotic proteins, transcription factors, growth factors, oncoproteins, tumor suppressor genes, receptors, and other proteins involved in cell proliferation, cellular differentiation, survival, angiogenesis, migration, and invasion, or other cellular processes involved in cancer. Various animal studies strongly advocate the potential role of MAG in controlling the growth of different tumors. However, not even one clinical study has investigated the efficacy of MAG. As MAG is obtained from Mother Nature, it could drastically economize the expenditure associated with this ever-growing dreadful disease. However, additional preclinical and clinical investigations are essential to proclaim the therapeutic potential of MAG that would help to bring this compound to the clinic.

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**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| AIF | apoptosis inducing factor |
| AMPK | AMP-activated protein kinase |
| Bak | Bcl-2 homologous antagonist/killer |
| Bax | Bcl-2-associated X protein |
| Bcl-2 | B-cell lymphoma 2 |
| Bcl-XL | B-cell lymphoma-extra large |
| Bid | BH3 interacting-domain death agonist |
| Ca (2+) | Calcium |
| CDC25A | cell division cycle 25 homolog A |
| CDK | cyclin-dependent kinase |
| Cip1 | CDK-interacting protein 1 |
| COX-2 | Cyclooxygenase-2 |
| cyt-c | cytochrome-c |
| DNA | Deoxyribo nucleic acid |
| DRS | Death receptor 5 EGFR: epidermal growth factor receptor |
| ERK | extracellular phosphorylated signal-regulated kinase |
| FoxO3 | Forkhead box O3 |
| GAS5 | growth arrest-specific 5 HIF-1α:hypoxia-inducible factors-1α |
| IGF-1 | Insulin-like growth factor 1 |
| IGFBP-5 | Insulin-like growth factor binding Protein-5 |
| iNOS | inducible nitric oxide synthase |
| Kip1 | Kinase inhibitory protein |
| 5-LO | 5-lipoxygenase |
| LOX | Lysyl oxidase |
| LT | Leukotriene |
| MDR | Multidrug resistance |
| MMP | Matrix metalloproteinases |
| mTOR | mammalian target of rapamycin |
| NF-κB | Nuclear factor kappa B |
| NSCLC | Non-small cell lung cancer cell lines |
PARP Poly ADP ribose polymerase
PCNA Proliferating cell nuclear antigen
P-gp Phosphorylated-glycoprotein
PI3K Phosphatidylinositol-4,5-bisphosphate 3-kinase
PKC protein kinase C
PLA2 phospholipase A2
PLC phospholipase C
PTEN phosphatase and tensin homolog
SOC Store-operated Ca (2+) channels
TNF-α Tumor necrosis factor-alpha
TRAIL TNF-related apoptosis-inducing ligand
uPA urokinase plasminogen activator
VEGF Vascular endothelial growth factor

References
1. Torre, L.A.; Bray, F.; Siegel, R.L.; Ferlay, J.; Lortet-Tieulent, J.; Jemal, A. Global cancer statistics, 2012. CA Cancer J. Clin. 2015, 65, 87–108. [CrossRef] [PubMed]
2. Sailo, B.L.; Banik, K.; Padmavathi, G.; Javadi, M.; Bordoloi, D.; Kunnumakkara, A.B. Tocotrienols: The promising analogues of vitamin E for cancer therapeutics. Pharmacol. Res. 2018, 130, 259–272. [CrossRef] [PubMed]
3. Kunnumakkara, A.B.; Sailo, B.L.; Banik, K.; Harsha, C.; Prasad, S.; Gupta, S.C.; Bharti, A.C.; Aggarwal, B.B. Chronic diseases, inflammation, and spices: How are they linked? J. Transl. Med. 2018, 16, 14. [CrossRef] [PubMed]
4. Khwairakpam, A.D.; Bordoloi, D.; Thakur, K.K.; Monisha, J.; Arfuso, F.; Sethi, G.; Mishra, S.; Kumar, A.P.; Kunnumakkara, A.B. Possible use of Punica granatum (Pomegranate) in cancer therapy. Pharmacol. Res. 2018, 133, 53–64. [CrossRef] [PubMed]
5. Padmavathi, G.; Roy, N.K.; Bordoloi, D.; Arfuso, F.; Mishra, S.; Sethi, G.; Bishayee, A.; Kunnumakkara, A.B. Butein in health and disease: A comprehensive review. Phytomedicine 2017, 25, 118–127. [CrossRef] [PubMed]
6. Kunnumakkara, A.B.; Bordoloi, D.; Padmavathi, G.; Monisha, J.; Roy, N.K.; Prasad, S.; Aggarwal, B.B. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. Br. J. Pharmacol. 2017, 174, 1325–1348. [CrossRef] [PubMed]
7. Roy, N.K.; Deka, A.; Bordoloi, D.; Mishra, S.; Kumar, A.P.; Sethi, G.; Kunnumakkara, A.B. The potential role of boswellic acids in cancer prevention and treatment. Cancer Lett. 2016, 377, 74–86. [CrossRef] [PubMed]
8. Li, F.; Sethi, G. Targeting transcription factor NF-kappaB to overcome chemoresistance and radioresistance in cancer therapy. Biochim. Biophys. Acta 2010, 1805, 167–180. [PubMed]
9. Manu, K.A.; Shannugam, M.K.; Li, F.; Chen, L.; Siveen, K.S.; Ahn, K.S.; Kumar, A.P.; Sethi, G. Simvastatin sensitizes human gastric cancer xenograft in nude mice to capecitabine by suppressing nuclear factor-kappa B-regulated gene products. J. Mol. Med. 2014, 92, 267–276. [CrossRef] [PubMed]
10. Liu, T.; Pan, Y.; Lai, R. New mechanism of magnolol and honokiol from Magnolia officinalis against Staphylococcus aureus. Nat. Prod. Commun. 2014, 9, 1307–1309. [PubMed]
11. Siveen, K.S.; Mustafa, N.; Li, F.; Kannaiyan, R.; Ahn, K.S.; Kumar, A.P.; Chng, W.J.; Sethi, G. Thymoquinone overcomes chemoresistance and enhances the anticancer effects of bortezomib through abrogation of NF-kappaB regulated gene products in multiple myeloma xenograft mouse model. Oncotarget 2014, 5, 634–648. [CrossRef] [PubMed]
12. Li, F.; Shannugam, M.K.; Siveen, K.S.; Wang, F.; Ong, T.H.; Loo, S.Y.; Swamy, M.M.; Mandal, S.; Kumar, A.P.; Goh, B.C.; et al. Garcinol sensitizes human head and neck carcinoma to cisplatin in a xenograft mouse model despite downregulation of proliferative biomarkers. Oncotarget 2015, 6, 5147–5163. [CrossRef] [PubMed]
13. Tahover, E.; Hubert, A.; Temper, M.; Salah, A.; Peretz, T.; Hamburger, T.; Uziely, B. An observational cohort study of bevacizumab and chemotherapy in metastatic colorectal cancer patients: Safety and efficacy with analysis by age group. Target. Oncol. 2015, 10, 55–63. [CrossRef] [PubMed]
14. Manu, K.A.; Shanmugam, M.K.; Ramachandran, L.; Li, F.; Siveen, K.S.; Chinnathambi, A.; Zayed, M.E.; Alharbi, S.A.; Arfuso, F.; Kumar, A.P.; et al. Isohamnetin augments the anti-tumor effect of capecitabine through the negative regulation of NF-kappaB signaling cascade in gastric cancer. *Cancer Lett.* 2015, 363, 28–36. [CrossRef] [PubMed]

15. Banik, K.; Harsha, C.; Bordoloi, D.; Laldhuksai Sailo, B.; Sethi, G.; Leong, H.C.; Arfuso, F.; Missha, S.; Wang, L.; Kumar, A.P.; et al. Therapeutic potential of gambogenic acid, a caged xanthone, to target cancer. *Cancer Lett.* 2018, 416, 75–86. [CrossRef] [PubMed]

16. Monisha, J.; Jaiswal, A.; Banik, K.; Choudhary, H.; Singh, A.K.; Bordoloi, D.; Kunnnumakkara, A.B. Cancer Cell Chemoresistance: A Prime Obstacle in Cancer Therapy. In *Cancer Cell Chemoresistance and Chemosensitization*; World Scientific: Singapore, 2018; ISBN 978-981-320-856-8.

17. Bordoloi, D.; Roy, N.K.; Monisha, J.; Padmavathi, G.; Kunnnumakkara, A.B. Multi-Targeted Agents in Cancer Cell Chemosensitization: What We Learnt from Curcumin Thus Far. *Recent Pat. Anti-Cancer Drug Discov.* 2016, 11, 67–97. [CrossRef]

18. Kunnnumakkara, A.B.; Nair, A.S.; Sung, B.; Pandey, M.K.; Aggarwal, B.B. Boswellic acid blocks signal transducers and activators of transcription 3 signaling, proliferation, and survival of multiple myeloma via the protein tyrosine phosphatase SHP-1. *Mol. Cancer Res.* 2009, 7, 118–128. [CrossRef] [PubMed]

19. Melnick, S.J. Developmental therapeutics: Review of biologically based CAM therapies for potential application in children with cancer: Part I. *J. Pediatr. Hematol. Oncol.* 2006, 28, 221–230. [CrossRef] [PubMed]

20. Deorukhkar, A.; Krishnan, S.; Sethi, G.; Aggarwal, B.B. Back to basics: How natural products can provide the basis for new therapeutics. *Expert Opin. Investig. Drugs* 2007, 16, 1753–1773. [CrossRef] [PubMed]

21. Rahmani, A.H.; Al Zohairy, M.A.; Aly, S.M.; Khan, M.A. Curcumin: A potential candidate in prevention of cancer via modulation of molecular pathways. *BioMed Res. Int.* 2014, 2014, 761608. [CrossRef] [PubMed]

22. Reed, J.C.; Pellecchia, M. Apoptosis-based therapies for hematologic malignancies. *Blood* 2005, 106, 408–418. [CrossRef] [PubMed]

23. Yang, S.F.; Weng, C.J.; Sethi, G.; Hu, D.N. Natural bioactives and phytochemicals serve in cancer treatment and prevention. *Evid.-Based Complement. Altern. Med.* 2013, 2013, 698190. [CrossRef] [PubMed]

24. Tang, C.H.; Sethi, G.; Kuo, P.L. Novel medicines and strategies in cancer treatment and prevention. *BioMed Res. Int.* 2014, 2014, 474078. [CrossRef] [PubMed]

25. Hsieh, Y.S.; Yang, S.F.; Sethi, G.; Hu, D.N. Natural bioactives in cancer treatment and prevention. *BioMed Res. Int.* 2015, 2015, 182835. [CrossRef] [PubMed]

26. Shanmugam, M.K.; Lee, J.H.; Chai, E.Z.; Kanchi, M.M.; Kar, S.; Arfuso, F.; Dharmarajan, A.; Kumar, A.P.; Ramar, P.S.; Looi, C.Y.; et al. Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds. *Semin. Cancer Biol.* 2016, 40–41, 35–47. [CrossRef] [PubMed]

27. Bishayee, A.; Sethi, G. Bioactive natural products in cancer prevention and therapy: Progress and promise. *Semin. Cancer Biol.* 2016, 40–41, 1–3. [CrossRef] [PubMed]

28. Yarla, N.S.; Bishayee, A.; Sethi, G.; Reddanna, P.; Kalle, A.M.; Dhananjaya, B.L.; Dowluru, K.S.; Chintala, R.; Duddukuri, G.R. Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. *Semin. Cancer Biol.* 2016, 40–41, 48–81. [CrossRef] [PubMed]

29. Shanmugam, M.K.; Warrier, S.; Kumar, A.P.; Sethi, G.; Arfuso, F. Potential Role of Natural Compounds as Anti-Angiogenic Agents in Cancer. *Curr. Vasc. Pharmacol.* 2017, 15, 503–519. [CrossRef] [PubMed]

30. Singh, S. From exotic spice to modern drug? *Cell* 2007, 130, 765–768. [CrossRef] [PubMed]

31. Newman, D.J.; Cragg, G.M.; Snader, K.M. Natural products as sources of new drugs over the period 1981–2002. *J. Nat. Prod.* 2003, 66, 1022–1037. [CrossRef] [PubMed]

32. Kunnnumakkara, A.B.; Bordoloi, D.; Harsha, C.; Banik, K.; Gupta, S.C.; Aggarwal, B.B. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. *Clin. Sci.* 2017, 131, 1781–1799. [CrossRef] [PubMed]

33. Harsha, C.; Banik, K.; Bordoloi, D.; Kunnnumakkara, A.B. Antulcer properties of fruits and vegetables: A mechanism based perspective. *Food Chem. Toxicol.* 2017, 108, Pt A, 104–119. [CrossRef]

34. Kunnnumakkara, A.B.; Sung, B.; Ravindran, J.; Diagaradjane, P.; Deorukhkar, A.; Dey, S.; Koca, C.; Yadav, V.R.; Tong, Z.; Gelovani, J.G.; et al. γ-tocotrienol inhibits pancreatic tumors and sensitizes them to gemcitabine treatment by modulating the inflammatory microenvironment. *Cancer Res.* 2010, 70, 8695–8705. [CrossRef] [PubMed]
35. Christodoulou, M.I.; Kontos, C.K.; Halabalaki, M.; Skaltsounis, A.L.; Scorilas, A. Nature promises new anticancer agents: Interplay with the apoptosis-related BCL2 gene family. Anti-Cancer Agents Med. Chem. 2014, 14, 375–399. [CrossRef]

36. Millimounou, F.M.; Dong, J.; Yang, L.; Li, J.; Li, X. Targeting apoptosis pathways in cancer and perspectives with natural compounds from mother nature. Cancer Prev. Res. 2014, 7, 1081–1107. [CrossRef] [PubMed]

37. Padmavathi, G.; Rathnakaram, S.R.; Monisha, J.; Bordoloi, D.; Roy, N.K.; Kunnumakkara, A.B. Potential of butein, a tetrahydroxychalcone to obliterate cancer. Phytomedicine 2015, 22, 1163–1171. [CrossRef] [PubMed]

38. Shen, J.; Ma, H.; Zhang, T.; Liu, H.; Hu, M. Magnolol Inhibits the Growth of Non-Small Cell Lung Cancer: A systematic review. Lung Cancer 2010, 68, 137–145. [CrossRef] [PubMed]

39. Jeong, S.J.; Koh, W.; Kim, B.; Kim, S.H. Are there new therapeutic options for treating lung cancer based on herbal medicines and their metabolites? J. Ethnopharmacol. 2011, 138, 652–661. [CrossRef] [PubMed]

40. Shanmugam, M.K.; Kannaiyan, R.; Sethi, G. Targeting cell signaling and apoptotic pathways by dietary agents: Role in the prevention and treatment of cancer. Nutr. Cancer 2011, 63, 161–173. [CrossRef] [PubMed]

41. Luo, L.; Nong Wang, J.; Kong, L.D.; Jiang, Q.G.; Tan, R.X. Antidepressant effects of Banxia Houpu decoction, a traditional Chinese medicinal empirical formula. J. Ethnopharmacol. 2000, 73, 277–281. [CrossRef]

42. Hsu, H.-Y.; Hsu, C.-S. Commonly Used Chinese Herb Formulas with Illustrations; Oriental Healing Arts Institute: Irvine, CA, USA, 1980; ISBN 9780941942034.

43. Sugaya, A.; Tsuda, T.; Obuchi, T.; Sugaya, E. Effect of Chinese herbal medicine “Hange-Koboku-To” on laryngeal reflex of cats and in other pharmacological tests. Planta Med. 1983, 47, 59–62. [CrossRef] [PubMed]

44. Iwasaki, K.; Wang, Q.; Seki, H.; Satoh, K.; Takek a, A.; Ari, H.; Sasaki, H. The effects of the traditional chinese medicine, “Banxia Houpu Tang (Hange-Koboku To)” on the swallowing reflex in Parkinson’s disease. Phytomedicine 2000, 7, 259–263. [CrossRef]

45. Fukushima, M. Profiles of effects of traditional oriental herbal medicines on central nervous systems in humans—assessment of saiboku-to and saiko-ka-ryukotsu-borei-to using EEG and pharmacokinetics of herbal medicine-derived ingredients as indices. Seisin Shinkeigaku Zasshi 1997, 99, 355–369. [PubMed]

46. Lee, Y.J.; Lee, Y.M.; Lee, C.K.; Jung, J.K.; Han, S.B.; Hong, J.T. Therapeutic applications of compounds in the Magnolia family. Pharmacol. Ther. 2011, 130, 157–176. [CrossRef] [PubMed]

47. Choi, J.H.; Ha, J.; Park, J.H.; Lee, J.Y.; Lee, Y.S.; Park, H.J.; Choi, J.W.; Masuda, Y.; Nakaya, K.; Lee, K.T. Costunolide triggers apoptosis in human leukemia U937 cells by depletion of intracellular thiols. Jpn. J. Cancer Res. 2002, 93, 1327–1333. [CrossRef] [PubMed]

48. Kang, J.S.; Lee, K.H.; Han, M.H.; Lee, H.; Ahn, J.M.; Han, S.B.; Han, G.; Lee, K.; Park, S.K.; Kim, H.M. Antiinflammatory activity of methanol extract isolated from stem bark of Magnolia kobus. Phytother. Res. 2008, 22, 883–888. [CrossRef] [PubMed]

49. Kong, C.W.; Tsai, K.; Chin, J.H.; Chan, W.L.; Hong, C.Y. Magnolol attenuates peroxidative damage and improves survival of rats with sepsis. Shock 2000, 13, 24–28. [CrossRef] [PubMed]

50. Jada, S.; Doma, M.R.; Singh, P.P.; Kumar, S.; Malik, F.; Sharma, A.; Khan, I.A.; Qazi, G.N.; Kumar, H.M. Design and synthesis of novel magnolol derivatives as potential antimicrobial and antiproliferative compounds. Eur. J. Med. Chem. 2012, 51, 35–41. [CrossRef] [PubMed]

51. Miali, M.; Basoli, V.; Carta, P.; Fabbri, D.; Dettori, M.A.; Cruciani, S.; Serra, P.A.; Delogu, G. Synthesis of magnolol and honokiol derivatives and their effect against hepatocarcinoma cells. PLoS ONE 2018, 13, e0192178. [CrossRef] [PubMed]

52. Shen, J.; Ma, H.; Zhang, T.; Liu, H.; Yu, L.; Li, G.; Li, H.; Hu, M. Magnolol Inhibits the Growth of Non-Small Cell Lung Cancer via Inhibiting Microtubule Polymerization. Cell. Physiol. Biochem. 2017, 42, 1789–1801. [CrossRef] [PubMed]

53. Chen, M.C.; Chen, Y.L.; Lee, C.F.; Hung, C.H.; Chou, T.C. Supplementation of Magnolol Attenuates Skeletal Muscle Atrophy in Bladder Cancer-Bearing Mice Undergoing Chemotherapy via Suppression of FoxO3 Activation and Induction of IGF-1. PLoS ONE 2015, 10, e0143594. [CrossRef] [PubMed]

54. Hagiwara, K.; Gailhouse, L.; Yasukawa, K.; Kosaka, N.; Ochiya, T. A robust screening method for dietary agents that activate tumour-suppressor microRNAs. Sci. Rep. 2015, 5, 14697. [CrossRef] [PubMed]

55. McKeown, B.T.; McDougall, L.; Catalli, A.; Hurta, R.A. Magnolol causes alterations in the cell cycle in androgen insensitive human prostate cancer cells in vitro by affecting expression of key cell cycle regulatory proteins. Nutr. Cancer 2014, 66, 1154–1164. [CrossRef] [PubMed]
56. Konoshima, T.; Kozuka, M.; Tokuda, H.; Nishino, H.; Iwashima, A.; Haruna, M.; Ito, K.; Tanabe, M. Studies on inhibitors of skin tumor promotion, IX. Neolignans from Magnolia officinalis. J. Nat. Prod. 1991, 54, 816–822. [CrossRef] [PubMed]
57. Lin, S.Y.; Chang, Y.T.; Liu, J.D.; Yu, C.H.; Ho, Y.S.; Lee, Y.H.; Lee, W.S. Molecular mechanisms of apoptosis induced by magnolol in colon and liver cancer cells. Mol. Carcinog. 2001, 32, 73–83. [CrossRef] [PubMed]
58. Li, M.; Zhang, F.; Wang, X.; Wu, X.; Zhang, B.; Zhang, N.; Wu, W.; Wang, Z.; Weng, H.; Liu, S.; et al. Magnolol inhibits growth of gallbladder cancer cells through the p53 pathway. Cancer Sci. 2015, 106, 1341–1350. [CrossRef] [PubMed]
59. Lin, S.Y.; Liu, J.D.; Chang, H.C.; Yeh, S.D.; Lin, C.H.; Lee, W.S. Magnolol suppresses proliferation of cultured human colon and liver cancer cells by inhibiting DNA synthesis and activating apoptosis. J. Cell. Biochem. 2002, 84, 532–544. [CrossRef] [PubMed]
60. Zhai, H.; Nakade, K.; Mitsumoto, Y.; Fukuyama, Y. Honokiol and magnolol induce Ca2+ mobilization in rat cortical neurons and human neuroblastoma SH-SY5Y cells. Eur. J. Pharmacol. 2003, 474, 199–204. [CrossRef] [PubMed]
61. Ikeda, K.; Sakai, Y.; Nagase, H. Inhibitory effect of magnolol on tumour metastasis in mice. Phytother. Res. 2003, 17, 933–937. [CrossRef] [PubMed]
62. O’Neil, M.J. The Merck Index—An Encyclopedia of Chemicals, Drugs, and Biologicals; Merck and Co. Inc.: Whitehouse Station, NJ, USA, 2006; ISBN 091191000X, ISBN 9780911910001.
63. Yang, C.; Zhi, X.; Xu, H. Advances on Semisynthesis, Total Synthesis, and Structure-Activity Relationships of Honokiol and Magnolol Derivatives. Mini Rev. Med. Chem. 2016, 16, 404–426. [CrossRef] [PubMed]
64. Lee, C.W.; Hu, S.C.; Yen, F.L.; Hsu, L.F.; Lee, I.T.; Lin, Z.C.; Tsai, M.H.; Huang, C.L.; Liang, C.J.; Chiang, Y.C. Magnolol Nanoparticles Exhibit Improved Water Solubility and Suppress TNF-alpha-Induced VCAM-1 Expression in Endothelial Cells. J. Biomed. Nanotechnol. 2017, 13, 255–268. [CrossRef] [PubMed]
65. National Center for Biotechnology Information: PubChem Compound Database. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/72300 (accessed on 5 July 2018).
66. Jin-Ping, S.; Zai-Kang, T.; Ri-Yan, Z. Study of quality of Hou Po. J. Nat. Prod. 1991, 54, 816–822. [CrossRef] [PubMed]
67. Tang, C.Y.; Lai, C.C.; Huang, P.H.; Yang, A.H.; Chiang, S.C.; Huang, P.C.; Tseng, K.W.; Huang, C.H. Magnolol inhibits growth of gallbladder cancer cells through the p53 pathway. Cancer Sci. 2015, 106, 1341–1350. [CrossRef] [PubMed]
68. Hoi, C.P.; Ho, Y.P.; Baum, L.; Chow, A.H. Neuroprotective effect of honokiol and magnolol, compounds from Magnolia officinalis, on beta-amyloid-induced toxicity in PC12 cells. Phytother. Res. 2010, 24, 1538–1542. [CrossRef] [PubMed]
69. Lee, S.; Khoo, C.; Halstead, C.W.; Huynb, T.; Bensousan, A. Liquid chromatographic determination of honokiol and magnolol in hou po (Magnolia officinalis) as the raw herb and dried aqueous extract. J. AOAC Int. 2007, 90, 1210–1218. [PubMed]
70. Schifano, F.; Guarino, V.; Papanti, D.G.; Baccarin, J.; Orsolini, L.; Corkery, J.M. Is there a potential of misuse for Magnolia officinalis compounds/metabolites? Hum. Psychopharmacol. 2017, 32. [CrossRef] [PubMed]
71. Kou, D.Q.; Jiang, Y.L.; Qin, J.H.; Huang, Y.H. Magnolol attenuates the inflammation and apoptosis through the activation of SIRT1 in experimental stroke rats. Pharmacol. Rep. 2017, 69, 642–647. [CrossRef] [PubMed]
72. Wang, J.J.; Zhao, R.; Liang, J.C.; Chen, Y. The antidiabetic and hepatoprotective effects of magnolol on diabetic rats induced by high-fat diet and streptozotocin. Acta Pharmaceutica Sinica 2014, 49, 476–481. [PubMed]
77. Sohn, E.J.; Kim, C.S.; Kim, Y.S.; Jung, D.H.; Jang, D.S.; Lee, Y.M.; Kim, J.S. Effects of magnolol (5,5′-diallyl-2,2′-dihydroxybiphenyl) on diabetic nephropathy in type 2 diabetic Goto-Kakizaki rats. *Life Sci.* 2007, 80, 468–475. [CrossRef] [PubMed]

78. Squires, R.F.; Ai, J.; Witt, M.R.; Kahnberg, P.; Saederup, E.; Sterner, O.; Nielsen, M. Honokiol and magnolol increase the number of [3H] muscimol binding sites three-fold in rat forebrain membranes in vitro using a filtration assay, by allosterically increasing the affinities of low-affinity sites. *Neurochem. Res.* 1999, 24, 1593–1602. [CrossRef] [PubMed]

79. Garrison, R.; Chambliss, W.G. Effect of a proprietary Magnolia and Phellodendron extract on weight management: A pilot, double-blind, placebo-controlled clinical trial. *Altern. Ther. Health Med.* 2006, 12, 50–54. [PubMed]

80. Oikawa, T.; Ito, G.; Koyama, H.; Hanawa, T. Prokinetic effect of a Kampo medicine, Hange-koboku-to (Banxia-houpo-tang), on patients with functional dyspepsia. *Phytomedicine* 2005, 12, 730–734. [CrossRef] [PubMed]

81. Chiou, L.C.; Ling, J.Y.; Chang, C.C. Chinese herb constituent beta-eudesmol alleviated the electroshock seizures in mice and electrographic seizures in rat hippocampal slices. *Neurosci. Lett.* 1997, 231, 171–174. [CrossRef]

82. Lee, Y.J.; Choi, D.Y.; Han, S.B.; Kim, Y.H.; Kim, K.H.; Hwang, B.Y.; Kang, J.K.; Lee, B.J.; Oh, K.W.; Hong, J.T. Inhibitory effect of ethanol extract of Magnolia officinalis on memory impairment and amyloidogenesis in a transgenic mouse model of Alzheimer's disease via regulating beta-secretase activity. *Phytother. Res.* 2012, 26, 1884–1892. [CrossRef] [PubMed]

83. Lin, Y.R.; Chen, H.H.; Ko, C.H.; Chan, M.H. Effects of honokiol and magnolol on acute and inflammatory pain models in mice. *Life Sci.* 2007, 81, 1071–1078. [CrossRef] [PubMed]

84. Kalman, D.S.; Feldman, S.; Feldman, R.; Schwartz, H.I.; Krieger, D.R.; Garrison, R. Effect of a proprietary Magnolia and Phellodendron extract on stress levels in healthy women: A pilot, double-blind, placebo-controlled clinical trial. *Nutr. J.* 2008, 7, 11. [CrossRef] [PubMed]

85. Mantani, N.; Hisanaga, A.; Kogure, T.; Kita, T.; Shimada, Y.; Terasawa, K. Four cases of panic disorder successfully treated with Kampo (Japanese herbal) medicines: Kami-shoyo-san and Hange-koboku-to. *Psychiatry Clin. Neurosci.* 2002, 56, 617–620. [CrossRef] [PubMed]

86. Nakazawa, T.; Yasuda, T.; Ohsawa, K. Metabolites of orally administered Magnolia officinalis extract in rats and man and its antidepressant-like effects in mice. *J. Pharm. Pharmacol.* 2003, 55, 1583–1591. [CrossRef] [PubMed]

87. Tsai, T.H.; Chou, C.J.; Chen, C.F. Pharmacokinetics and brain distribution of magnolol in the rat after intravenous bolus injection. *J. Pharm. Pharmacol.* 1996, 48, 57–59. [CrossRef] [PubMed]

88. Wang, X.; Duan, X.; Yang, G.; Zhang, X.; Deng, L.; Zheng, H.; Deng, C.; Wen, J.; Wang, N.; Peng, C.; et al. Honokiol crosses BBB and BCSFB, and inhibits brain tumor growth in rat 9L intracerebral gliosarcoma model and human U251 xenograft glioma model. *PLoS ONE* 2011, 6, e18490. [CrossRef] [PubMed]

89. Kao, Y.H.; Jawan, B.; Sun, C.K.; Goto, S.; Lin, Y.C.; Hung, C.T.; Pan, M.C.; Hsu, L.W.; Cheng, Y.F.; Lai, C.Y.; et al. High concentration of magnolol induces hepatotoxicity under serum-reduced conditions. *Phytomedicine* 2010, 17, 469–474. [CrossRef] [PubMed]

90. Liu, Z.; Zhang, X.; Cui, W.; Zhang, X.; Li, N.; Chen, J.; Wong, A.W.; Roberts, A. Evaluation of short-term and subchronic toxicity of magnolia bark extract in rats. *Regul. Toxicol. Pharmacol.* 2007, 49, 160–171. [CrossRef] [PubMed]

91. Coppola, M.; Mondola, R. Potential use of Magnolia officinalis bark polyphenols in the treatment of cannabis dependence. *Med. Hypotheses* 2014, 83, 673–676. [CrossRef] [PubMed]

92. Park, E.J.; Kim, S.Y.; Zhao, Y.Z.; Sohn, D.H. Honokiol reduces oxidative stress, c-jun-NH2-terminal kinase phosphorylation and protects against glycochenodeoxycholic acid-induced apoptosis in primary cultured rat hepatocytes. *Planta Med.* 2006, 72, 661–664. [CrossRef] [PubMed]

93. Jiang, X.; Wang, X. Cytochrome C-mediated apoptosis. *Annu. Rev. Biochem.* 2004, 73, 87–106. [CrossRef] [PubMed]

94. Ledgerwood, E.C.; Morison, I.M. Targeting the apoptosome for cancer therapy. *Clin. Cancer Res.* 2009, 15, 420–424. [CrossRef] [PubMed]

95. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell* 2000, 100, 57–70. [CrossRef]
96. Taylor, R.C.; Cullen, S.P.; Martin, S.J. Apoptosis: Controlled demolition at the cellular level. *Nat. Rev. Mol. Cell Biol.* 2008, 9, 231–241. [CrossRef] [PubMed]

97. Fischer, U.; Janssen, K.; Schulze-Osthoff, K. Cutting-edge apoptosis-based therapeutics: A panacea for cancer? *BioDrugs* 2007, 21, 273–297. [CrossRef] [PubMed]

98. Yang, S.E.; Hsieh, M.T.; Tsai, T.H.; Hsu, S.L. Effector mechanism of magnolol-induced apoptosis in human lung squamous carcinoma CH27 cells. *Br. J. Pharmacol.* 2003, 138, 193–201. [CrossRef] [PubMed]

99. Chen, F.; Wang, T.; Wu, Y.F.; Gu, Y.; Xu, X.L.; Zheng, S.; Hu, X. Honokiol: A potent chemotherapy candidate for human colorectal carcinoma. *World J. Gastroenterol.* 2004, 10, 3459–3463. [CrossRef] [PubMed]

100. Battle, T.E.; Arbiser, J.; Frank, D.A. The natural product honokiol induces caspase-dependent apoptosis in B-cell chronic lymphocytic leukemia (B-CLL) cells. *Blood* 2005, 106, 690–697. [CrossRef] [PubMed]

101. Huang, S.H.; Chen, Y.; Tung, P.Y.; Wu, J.C.; Wu, J.M.; Wang, S.M. Mechanisms for the inhibition of osteoclastogenesis. *Blood* 2003, 101, 5112–5121. [CrossRef] [PubMed]

102. Battle, T.E.; Arbiser, J.; Frank, D.A. The natural product honokiol induces caspase-dependent apoptosis in B-cell chronic lymphocytic leukemia (B-CLL) cells. *Blood* 2005, 106, 690–697. [CrossRef] [PubMed]

103. Lee, S.J.; Park, S.S.; Lee, U.S.; Kim, W.J.; Moon, S.K. Signaling pathway for TNF-alpha-induced MMP-9 activation, leading to potentiation of apoptosis, inhibition of invasion, and suppression of osteoclastogenesis. *Mol. Cancer Ther.* 2008, 7, 3306–3317. [CrossRef] [PubMed]

104. Kunnumakkara, A.B.; Ichikawa, H.; Anand, P.; Mohankumar, C.J.; Hema, P.S.; Nair, M.S.; Aggarwal, B.B. Coronarin D, a labdane diterpen, inhibits both constitutive and inducible nuclear factor-kappaB pathway activation, leading to potentiation of apoptosis, inhibition of invasion, and suppression of osteoclastogenesis. *Mol. Cancer Ther.* 2008, 7, 3306–3317. [CrossRef] [PubMed]

105. Kunnumakkara, A.B.; Nair, A.S.; Ahn, K.S.; Pandey, M.K.; Yi, Z.; Liu, M.; Aggarwal, B.B. Gossypin, a pentahydroxy glucosyl flavone, inhibits the transforming growth factor beta-activated kinase-1-mediated NF-kappaB activation pathway, leading to potentiation of apoptosis, suppression of invasion, and abrogation of osteoclastogenesis. *Blood* 2007, 109, 5112–5121. [CrossRef] [PubMed]
116. Liu, Y.; Cao, W.; Zhang, B.; Liu, Y.Q.; Wang, Z.Y.; Wu, Y.P.; Yu, X.J.; Zhang, X.D.; Ming, P.H.; Zhou, G.B.; et al. The natural compound magnolol inhibits invasion and exhibits potential in human breast cancer therapy. *Sci. Rep.* 2013, 3, 3098. [CrossRef] [PubMed]

117. Ahn, K.S.; Sethi, G.; Shishodia, S.; Sung, B.; Arbiser, J.L.; Aggarwal, B.B. Honokiol potentiates apoptosis, suppresses osteoclastogenesis, and inhibits invasion through modulation of nuclear factor-kappaB activation pathway. *Mol. Cancer Res.* 2006, 4, 621–633. [CrossRef] [PubMed]

118. Seo, J.U.; Kim, M.H.; Kim, H.M.; Jeong, H.J. Anticancer potential of magnolol for lung cancer treatment. *Arch. Pharm. Res.* 2011, 34, 625–633. [CrossRef] [PubMed]

119. Kang, Y.J.; Park, H.J.; Chung, H.J.; Min, H.Y.; Park, E.J.; Lee, M.A.; Shin, Y.; Lee, S.K. Wnt/beta-catenin signaling mediates the antitumor activity of magnolol in colorectal cancer cells. *Mol. Pharmacol.* 2012, 82, 168–177. [CrossRef] [PubMed]

120. Li, H.B.; Yi, X.; Gao, J.M.; Ying, X.X.; Guan, H.Q.; Li, J.C. Magnolol-induced death via autophagy but not apoptosis. *Arch. Pharm. Res.* 2007, 30, 1566–1574. [CrossRef] [PubMed]

121. Kumar, S.; Guru, S.K.; Pathania, A.S.; Kumar, A.; Bhushan, S.; Malik, F. Autophagy triggered by magnolol derivative negatively regulates angiogenesis. *Cell Death Dis.* 2013, 4, e889. [CrossRef] [PubMed]

122. Lee, S.J.; Cho, Y.H.; Park, K.; Kim, E.J.; Jung, K.H.; Park, S.S.; Kim, W.J.; Moon, S.K. Magnolol elicits activation of the extracellular signal-regulated kinase pathway by inducing p27KIP1-mediated G2/M phase cell cycle arrest in human urinary bladder cancer cells. *Biochem. Pharmacol.* 2008, 75, 2289–2300. [CrossRef] [PubMed]

123. Chen, M.C.; Lee, C.F.; Huang, W.H.; Chou, T.C. Magnolol suppresses hypoxia-induced angiogenesis via inhibition of HIF-1alpha/VEGF signaling pathway in human bladder cancer cells. *Biochem. Pharmacol.* 2013, 85, 1278–1287. [CrossRef] [PubMed]

124. Chen, L.C.; Tu, S.H.; Huang, C.S.; Chen, C.S.; Ho, C.T.; Lin, H.W.; Lee, C.H.; Chang, H.W.; Chang, C.H.; Wu, C.H.; et al. Human breast cancer cell metastasis is attenuated by lysyl oxidase inhibitors through down-regulation of focal adhesion kinase and the paxillin-signaling pathway. *Breast Cancer Res. Treat.* 2012, 134, 989–1004. [CrossRef] [PubMed]

125. Hou, X.; Yuan, X.; Zhang, B.; Wang, S.; Chen, Q. Screening active anti-breast cancer compounds from Cortex Magnolia officinalis by 2D LC-MS. *J. Sep. Sci.* 2013, 36, 706–712. [CrossRef] [PubMed]

126. Zhou, Y.; Bi, Y.; Yang, C.; Yang, J.; Jiang, Y.; Meng, F.; Yu, B.; Khan, M.; Ma, T.; Yang, H. Magnolol induces apoptosis in MCF-7 human breast cancer cells through G2/M phase arrest and caspase-independent pathway. *Arch. Pharm. Res.* 2013, 36, 755–762. [CrossRef] [PubMed]

127. Li, M.; Hu, S.; Chen, X.; Wang, R.; Bai, X. Research on major antitumor active components in Zi-Cao-Cheng-Qi decoction based on hollow fiber cell fishing with high performance liquid chromatography. *J. Pharm. Biomed. Anal.* 2018, 149, 9–15. [CrossRef] [PubMed]

128. Nabekura, T.; Hiroi, T.; Kawasaki, T.; Uwai, Y. Effects of natural nuclear factor-kappa B inhibitors on anticancer drug efflux transporter human P-glycoprotein. *Biomed. Pharmacother.* 2015, 70, 140–145. [CrossRef] [PubMed]

129. Syu, W.J.; Shen, C.C.; Lu, J.J.; Lee, G.H.; Sun, C.M. Antimicrobial and cytotoxic activities of neolignans from Magnolia officinalis. *Chem. Biodivers.* 2004, 1, 530–537. [CrossRef] [PubMed]

130. Zhang, F.H.; Ren, H.Y.; Shen, J.X.; Zhang, X.Y.; Ye, H.M.; Shen, D.Y. Magnolol suppresses the proliferation and invasion of cholangiocarcinoma cells via inhibiting the NF-kappaB signaling pathway. *Biomed. Pharmacother.* 2017, 94, 474–480. [CrossRef] [PubMed]

131. Hsu, Y.F.; Lee, T.S.; Lin, S.Y.; Hsu, S.P.; Juang, S.H.; Hsu, Y.H.; Zhong, W.B.; Lee, W.S. Involvement of Ras/Raf-1/ERK actions in the magnolol-induced upregulation of p21 and cell-cycle arrest in colon cancer cells. *Mol. Carcinog.* 2007, 46, 275–283. [CrossRef] [PubMed]

132. Park, J.B.; Lee, M.S.; Cha, E.Y.; Lee, J.S.; Sul, J.Y.; Song, I.S.; Kim, J.Y. Magnolol-induced apoptosis in HCT-116 colon cancer cells is associated with the AMP-activated protein kinase signaling pathway. *Biol. Pharm. Bull.* 2012, 35, 1614–1620. [CrossRef] [PubMed]

133. Chen, L.C.; Lee, W.S. P27/Kip1 is responsible for magnolol-induced U373 apoptosis in vitro and in vivo. *J. Agric. Food Chem.* 2013, 61, 2811–2819. [CrossRef] [PubMed]

134. Nagase, H.; Ikeda, K.; Sakai, Y. Inhibitory effect of magnolol and honokiol from Magnolia obovata on human fibrosarcoma HT-1080. Invasiveness in vitro. *Planta Med.* 2001, 67, 705–708. [CrossRef] [PubMed]
135. Rasul, A.; Yu, B.; Khan, M.; Zhang, K.; Iqbal, F.; Ma, T.; Yang, H. Magnolol, a natural compound, induces apoptosis of SGC-7901 human gastric adenocarcinoma cells via the mitochondrial and PI3K/Akt signaling pathways. *Int. J. Oncol.* **2012**, *40*, 1153–1161. [CrossRef] [PubMed]

136. Cheng, Y.C.; Hueng, D.Y.; Huang, H.Y.; Chen, J.Y.; Chen, Y. Magnolol and honokiol exert a synergistic anti-tumor effect through autophagy and apoptosis in human glioblastomas. *Oncotarget* **2016**, *7*, 29116–29130. [CrossRef] [PubMed]

137. Hamasaki, Y.; Kobayashi, I.; Zaitu, M.; Tsuji, K.; Kita, M.; Hayasaki, R.; Muro, E.; Yamamoto, S.; Matsuo, M.; Ichimaru, T.; et al. Magnolol inhibits leukotriene synthesis in rat basophilic leukemia-2H3 cells. *Planta Med.* **1999**, *65*, 222–226. [CrossRef] [PubMed]

138. Li, H.; Li, J.; Zhang, Y.J.; Jin, W.; Guo, X.; Li, N.; Ma, T.; Huo, Q.; Wu, C. Transglycosylation of neolignans by enzymatic synthesis and evaluation of their antitumor activity. *J. South. Med. Univ.* **2015**, *35*, 1570–1574.

139. Liu, H.M.; Zhao, S.R.; Huan, Q.; Ma, T.; Niu, H.; Lee, J.K.; Hong, Y.S.; Wu, C.Z. A new dimeric neolignan from Magnolia grandiflora L. seeds. *Arch. Pharm. Res.* **2015**, *38*, 1066–1071. [CrossRef] [PubMed]

140. Li, J.; Zhang, Y.J.; Jin, B.F.; Su, X.J.; Tao, Y.W.; She, Z.G.; Lin, Y.C. 1H and 13C NMR assignments for two lignans from the heartwood of Streblus asper. *Magn. Reson. Chem.* **2008**, *46*, 497–500. [CrossRef] [PubMed]

141. Di Micco, S.; Pulvirenti, L.; Bruno, I.; Terracciano, S.; Russo, A.; Vaccaro, M.C.; Ruggiero, D.; Muccilli, V.; Cardullo, N.; Tringali, C.; et al. Identification by Inverse Virtual Screening of magnolol-based scaffold as new tankyrase-2 inhibitors. *Bioorg. Med. Chem.* **2018**, *26*, 3953–3957. [CrossRef] [PubMed]

142. Liu, Y.; Tong, Y.; Yang, X.; Li, F.; Zheng, L.; Liu, W.; Wu, J.; Ou, R.; Zhang, G.; Hu, M.; et al. Novel histone deacetylase inhibitors derived from Magnolia officinalis significantly enhance TRAIL-induced apoptosis in non-small cell lung cancer. *Pharmacol. Res.* **2016**, *111*, 113–125. [CrossRef] [PubMed]

143. Tsai, J.R.; Chong, I.W.; Chen, Y.H.; Hwang, J.J.; Yin, W.H.; Chen, H.L.; Chou, S.H.; Chiu, C.C.; Liu, P.L. Magnolol induces apoptosis via caspase-independent pathways in non-small cell lung cancer cells. *Arch. Pharm. Res.* **2014**, *37*, 548–557. [CrossRef] [PubMed]

144. You, Q.; Li, M.; Jiao, G. Magnolol induces apoptosis via activation of both mitochondrial and death receptor pathways in A375-S2 cells. *Arch. Pharm. Res.* **2009**, *32*, 1789–1794. [CrossRef] [PubMed]

145. Hsieh, S.F.; Chou, C.T.; Liang, W.Z.; Kuo, C.C.; Wang, J.L.; Hao, L.J.; Jan, C.R. The effect of magnolol on Ca(2+) homeostasis and its related physiology in human oral cancer cells. *Arch. Oral Biol.* **2018**, *89*, 49–54. [CrossRef] [PubMed]

146. Chuang, T.C.; Hsu, S.C.; Cheng, Y.T.; Shao, W.S.; Wu, K.; Fang, G.S.; Ou, C.C.; Wang, V. Magnolol down-regulates HER2 gene expression, leading to inhibition of HER2-mediated metastatic potential in ovarian cancer cells. *Cancer Lett.* **2011**, *311*, 11–19. [CrossRef] [PubMed]

147. Han, H.K.; Van Anh, L.T. Modulation of P-glycoprotein expression by honokiol, magnolol and 4-O-methylhonokiol, the bioactive components of Magnolia officinalis. *Anticancer Res.* **2012**, *32*, 4445–4452. [PubMed]

148. McKeown, B.T.; Hurta, R.A. Magnolol affects expression of IGF-1 and associated binding proteins in human prostate cancer cells in vitro. *Anticancer Res.* **2014**, *34*, 6333–6338. [PubMed]

149. Lee, D.H.; Szczepanski, M.J.; Lee, Y.J. Magnolol induces apoptosis via inhibiting the EGFR/PI3K/Akt signaling pathway in human prostate cancer cells. *J. Cell. Biochem.* **2009**, *106*, 1113–1122. [CrossRef] [PubMed]

150. Hwang, E.S.; Park, K.K. Magnolol suppresses metastasis via inhibition of invasion, migration, and matrix metalloproteinase-2/-9 activities in PC-3 human prostate carcinoma cells. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 961–967. [CrossRef] [PubMed]
154. Wang, T.H.; Chan, C.W.; Fang, J.Y.; Shih, Y.M.; Liu, Y.W.; Wang, T.V.; Chen, C.Y. 2-O-Methylmagnolol upregulates the long non-coding RNA, GAS5, and enhances apoptosis in skin cancer cells. *Cell Death Dis.* 2017, 8, e2638. [CrossRef] [PubMed]

155. Kuo, D.H.; Lai, Y.S.; Lo, C.Y.; Cheng, A.C.; Wu, H.; Pan, M.H. Inhibitory effect of magnolol on TPA-induced skin inflammation and tumor promotion in mice. *J. Agric. Food Chem.* 2010, 58, 5777–5783. [CrossRef] [PubMed]

156. Chilampalli, C.; Guillermo, R.; Zhang, X.; Kaushik, R.S.; Young, A.; Zeman, D.; Hildreth, M.B.; Fahmy, H.; Dwivedi, C. Effects of magnolol on UVB-induced skin cancer development in mice and its possible mechanism of action. *BMC Cancer* 2011, 11, 456. [CrossRef] [PubMed]

157. Chilampalli, C.; Zhang, X.; Kaushik, R.S.; Young, A.; Zeman, D.; Hildreth, M.B.; Fahmy, H.; Dwivedi, C. Chemopreventive effects of combination of honokiol and magnolol with alpha-santalol on skin cancer developments. *Drug Discov. Ther.* 2013, 7, 109–115. [PubMed]

158. Khwairakpam, A.D.; Monisha, J.; Banik, K.; Choudhary, H.; Sharma, A.; Bordoloi, D.; Kunnumakkara, A.B. Chemoresistance in Brain Cancer and Different Chemosensitization Approaches. In *Cancer Cell Chemoresistance and Chemosensitization*; World Scientific: Singapore, 2018; pp. 107–127. ISBN 978-981-320-856-8.

159. Singh, A.K.; Roy, N.K.; Anip, A.; Banik, K.; Monisha, J.; Bordoloi, D.; Kunnumakkara, A.B. Different methods to inhibit chemoresistance in Hepatocellular carcinoma. In *Cancer Cell Chemoresistance and Chemosensitization*; World Scientific: Singapore, 2018; pp. 378–398. ISBN 978-981-320-856-8.

160. Padmavathi, G.; Monisha, J.; Banik, K.; Thakur, K.K.; Choudhary, H.; Bordoloi, D.; Kunnumakkara, A.B. Different chemosensitization approaches to overcome chemoresistance in prostate cancer. In *Cancer Cell Chemoresistance and Chemosensitization*; World Scientific: Singapore, 2018; pp. 583–613. ISBN 978-981-320-856-8.

161. Javadi, M.; Roy, N.K.; Sharma, A.; Banik, K.; Ganesan, P.; Bordoloi, D.; Kunnumakkara, A.B. Chemoresistance and chemosensitization in Melanoma. In *Cancer Cell Chemoresistance and Chemosensitization*; World Scientific: Singapore, 2018; pp. 479–527. ISBN 978-981-320-856-8.

162. Kapoor, V.K.; McMichael, A.J. Gallbladder cancer: An ‘Indian’ disease. *Natl. Med. J. India* 2003, 16, 209–213. [PubMed]

163. Banik, K.; Sailo, B.L.; Thakur, K.K.; Jaiswal, A.; Monisha, J.; Bordoloi, D.; Kunnumakkara, A.B. Potential of different chemosensitizers to overcome chemoresistance in cervical cancer. In *Cancer Cell Chemoresistance and Chemosensitization*; World Scientific: Singapore, 2018; pp. 163–179. ISBN 978-981-320-856-8.

164. Sailo, B.L.; Bordoloi, D.; Banik, K.; Khwairakpam, A.D.; Roy, N.K.; Prakash, J.; Kunnumakkara, A.B. Therapeutic strategies for chemosensitization of renal cancer. In *Cancer Cell Chemoresistance and Chemosensitization*; World Scientific: Singapore, 2018; pp. 615–639. ISBN 978-981-320-856-8.

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