Available online at www.sciencedirect.com

ScienceDirect

Journal of Nutritional Biochemistry 110 (2022) 109147

Journal of Nutritional Biochemistry

REVIEW ARTICLE

Crosstalk between xanthine oxidase (XO) inhibiting and cancer chemotherapeutic properties of comestible flavonoids- a comprehensive update

Md Sohanur Rahaman[a,c], Md Afjalus Siraj[b], Md Arman Islam[a], Prayas Chakma Shanto[a,c], Ordha Islam[a], Md Amirul Islam[a,**], Jesus Simal-Gandara[d,*]

[a] Pharmacy Discipline, Life Science School, Khulna University, Khulna, Bangladesh
[b] Department of Pharmaceutical Sciences, Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, Hilo, HI, USA
[c] Department of Regenerative Medicine, College of Medicine, Soonchunhyang University, Cheonan, Republic of Korea
[d] Universidade de Vigo, Nutrition and Bromatology Group, Analytical Chemistry and Food Science Department, Faculty of Science, E32004 Ourense, Spain

Received 3 June 2021; received in revised form 17 December 2021; accepted 10 August 2022

Abstract

Gout is an inflammatory disease caused by metabolic disorder or genetic inheritance. People throughout the world are strongly dependent on ethnomedicine for the treatment of gout and some receive satisfactory curative treatment. The natural remedies as well as established drugs derived from natural sources or synthetically made exert their action by mechanisms that are closely associated with anticancer treatment mechanisms regarding inhibition of xanthine oxidase, feedback inhibition of *de novo* purine synthesis, depolymerization and disappearance of microtubule, inhibition of NF-κB activation, induction of TRAIL, promotion of apoptosis, and caspase activation and proteasome inhibition. Some anti-gout and anticancer novel compounds interact with same receptors for their action, *e.g.*, colchicine and colchicine analogues. Dietary flavonoids, *i.e.*, chrysin, kaempferol, quercetin, fisetin, pelargonidin, apigenin, luteolin, myricetin, isorhamnetin, phloretinetc etc. have comparable IC_{50} values with established anti-gout drug and effective against both cancer and gout. Moreover, a noticeable number of newer anticancer compounds have already been isolated from plants that have been using by local traditional healers and herbal practitioners to treat gout. Therefore, the anti-gout plants might have greater potentiality to become selective candidates for screening of newer anticancer leads.
© 2022 The Author(s). Published by Elsevier Inc.
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Keywords: Xanthine oxidase; anticancer; flavonoids; anti-gout; chemotherapeutic.

1. Introduction

Gout is a metabolic disorder characterized by a high level of uric acid in blood which causes deposition of sodium urate crystals in tissues, especially in the joints [1]. The deposition of urate crystals initiates inflammatory arthritis recognized by a red, tender and swollen joint [2]. This inflammatory process is triggered by the infiltration of granulocytes that phagocytize the urate crystals and the reactive oxygen species (ROS) generated by this process, which in turn leads to tissue damage, and release of lysosomal enzyme, eventually evoking inflammatory response [1]. Uric acid is the main substance responsible for gout which is the end product of purine metabolism [3]. In human, it is formed from purine primarily by the xanthine oxidase (XO)-catalyzed oxidation of hypoxanthine and xanthine [4]. One of the mechanisms of gout treatment is to block the XO enzyme which will inhibit the oxidation of hypoxanthine and xanthine and thereby subsequent production of uric acid [1,4]. In this context, allopurinol is useful and brings relief to the victims of this painful condition [5]. Anti-gout drug allopurinol was first synthesized and reported in 1956 by Roland K. Robins, in a search for antineoplastic agents [6], but it was devoid of cytotoxicity [5].

However, a mysterious relationship between gout and cancer progression has been observed [7,8]. Increased uric acid production, mainly coming from excessive purine metabolism to provide fuel for uncontrolled cell proliferation, has shown influential role in various human diseases including gout [9,10]. In tumor cells, it is observed that purines and enzymes for de novo purine biosynthesis are increased [11] and hence they became targets for cancer treatment [12,13]. On the other hand, although the role of uric acid as a systemic antioxidant is documented, its pro-inflammatory actions have been suspected to bear a signifi-

* Corresponding author at: Jesus Simal-Gandara, Nutrition and Bromatology Group, Department of Analytical and Food Chemistry, Faculty of Food Science and Technology, University of Vigo-Ourense Campus, E32004 Ourense, Spain.
** Corresponding author at: Pharmacy Discipline, Life Science School, Khulna University, Khulna 9208, Bangladesh
E-mail addresses: ma.islam@pharm.ku.ac.bd (M.A. Islam), jsimal@uvigo.es (J. Simal-Gandara).

https://doi.org/10.1016/j.jnutbio.2022.109147
0955-2863/© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

cant role in cancer pathogenesis [14]. Especially, enhanced serum urate level and the dominant monosodium form of uric acid have been observed to possess a firm correlation with increasing number of premature cancer associated death [15–17]. As far as the pro-oxidant role of uric acid is concerned, via mediating the generation of ROS and inflammation, it assists tumorigenesis through penetrating normal cells and progressing tumor cell proliferation, migration, and survival [18]. One of the vital links between uric acid and cancer includes metabolic syndrome, which is associated with chronic inflammation, insulin resistance, hypertension, and abnormal lipid levels [19]. Metabolic syndrome raises serum uric acid (SUA) level which is also known as hyperuricemia. Previously it was reported, hyperuricemia is associated with increased number of cancer incidence and mortality [20]. Moreover, enhanced level of SUA has specific association with pro-inflammatory mediators, *i.e.*, C-Reactive Protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [14]. Patients with elevated levels of CRP have shown to lose pro-oxidant-antioxidant balance, and therefore are more prone to develop several cancers like colorectal, breast and urological cancers [21–24]. The inflammatory cytokine IL-6 is known for its presence in tumor microenvironment, where it is involved in cancer cell proliferation, angiogenesis and metastasis via affecting signal transducer and activator of transcription 3 (STAT3), mitogen activated protein kinase (MAPK), and protein kinase B (Akt) signaling pathways [25]. One of the major mediators of inflammation, TNF-α is a known endogenous tumor promoter and is associated with almost all parts in the process of tumorigenesis [26].

Several secondary metabolites from natural sources have been reported for their anti-gout properties. For example, colchicine; an alkaloid, generally derived from *Colchicum autumnale* provides dramatic relief from the attack of gout [4]. There are some other plants that contain colchicine such as *Colchicum luteum, Iphegenia indica, Glorisa superba, Gloriosa casuariana* and *Gloriosa vuchuria* etc. [27–31]. The anti-gout effect of *Colchicum autumnale* was known from the ancient era and Arabian physicians employed its root in gout treatment [5]. Colchicine, the antimitotic agent can arrest mitotic cell division in the metaphase by inhibiting spindle formation. By binding to tubulin, colchicine mediates depolymerization and disappearance of the fibrillar microtubules in granulocyte and other motile cells and inhibits the migration of granulocytes into the inflamed area of gout that results a decreased metabolic and phagocytic activity of granulocyte to exert anti-gout action [4]. This mechanism is much similar to the mechanism of anticancer agents like, podophyllotoxin [5] and vinca alkaloids [4]. Colchicine was tried for cancer chemotherapy but abandoned due to high toxicity [32]. Nevertheless, colchicine analogues share a common binding site on tubulin and demonstrate anticancer actions with some other natural compounds such as flavanols, combretastatins, etc. [33]. In addition to their remarkable antioxidant action, flavonoids are well capable to reduce oxidative insults through inactivation of enzymes, *e.g.*, nitric oxide synthase, phospholipase, and XO [34]. As, our enzyme of interest, XO raises during oxidative stress, cancer, and inflammatory gout attacks [35,36] and recent studies have been showed, alike chemotherapeutic agents long-term usage of prescribed anti-gout medications elevates the risk of common cancers like leukemia, non-hodgkin's, breast, and cervical cancers [37,38], flavonoids from natural sources might have remarkable contributions in managing diseases like cancers and gout either alone or in combination with mainstream drugs.

However, flavonoids with more planar chemical formation have shown better XO inhibitory activity [34]. These molecules are abandoned into edible sources originated from nature and bearing numerous potentials for their already reported excellent anti-gout and anti-inflammatory actions [39]. Previously, isolated bioactive flavonoids from edible plants, *e.g.*, apigenin, chrysin, lutenin, quarcetin, kaempferol, myricetin, have shown to exhibit remarkable XO inhibitory activity [40–42]. As a consequence of XO inhibition, the level of xanthine and hypoxanthine increases that initiates feedback to block *de novo* purine biosynthesis [32], which is also an essential treatment pathway for some of the antineoplastic drugs like 6-thioguanine and mercaptopurine [1,4]. These natural XO inhibitors have already been proven to exert anti-proliferative activity in *in vitro* studies against a number of cancer cell lines [43–46]. Therefore, XO inhibitory flavonoids from the dietary anti-gout supplements might be significant candidates in developing novel anti-cancer agents as well. Besides, in order to evaluate chemo preventive actions of these dietary sources, trail based research has become a great demand of time. The proposed anti-cancer mechanisms from anti-gout dietary sources are schematically illustrated in Figure 1. In this review, attempts has been made to correlate gout and cancer treatment mechanisms and establish the anti-gout natural resources as one of the promising sources of anticancer agents with exemplification of potential edible plants along with their supplementary formulations widely used in gout treatment.

2. Methodology

Google Scholar, PubMed, and Web of knowledge were the starting point to gather information on XO inhibitory flavonoid molecules together with their potential roles on anticancer activities. Other relevant sources, *e.g.*, books and journal articles, were also considered. The flavonoids previously showed both remarkable XO inhibitory as well as anticancer activities were taken into account for this study. However, 15 flavonoids were reported from 500 published articles according to their correlative actions on cancer and inflammatory disorders. Forty promising tropical plant species were found out based on their traditional usages as dietary supplements for gout and arthritis treatment. Presence of numerous flavonoids into these species which would suppose to be responsible for their bioactivity was also enlisted through extensive literature search.

3. XO inhibiting properties of flavonoids

Flavonoids are commonly natural products being mostly present in dietary sources have diversified health benefits [47,48]. Generally, their potential activity is the dose dependent or independent inhibition of oxidative and reductive enzymes, *e.g.*, XO, cyclo-oxygenase, aldose reductase, lipo-oxygenase, ATPase, and cytochrome p450 to produce ROS and thus protecting our body [49–52]. The unique dual phenolic ring system of flavonoids mimicking the original ligand's binding properties of these enzymes and shut down their induction [53,54].

XO is a homodimer protein (MW=290 KD) with one molybdopterin and one FAD cofactor for each monomer. The substrate binding and oxidation take place at molybdopterin site [55]. Several amino acid residues, *e.g.*, Arg 880, Phe 1,009, Phe 914, The 1,010, Glu 1,261 of this binding site, play a vital role for substrate binding through electrostatic interaction and hydrogen bonding [53]. It was reported that C-3, C-3′, C-4′, C-5, and C-7 hydroxyl groups on the flavonoids capable to form quinonoid compounds in biological systems are mostly responsible for inhibition of the enzyme XO [54,56]. In an *in vitro* simulation study, two flavonoids galangin and pinobanksin were found to form aromatic sandwich interaction with the amino acids residues of the active site of XO leading to inactivation [57]. To date, there were several studies reported in the literature to determine the inhibitory activ-

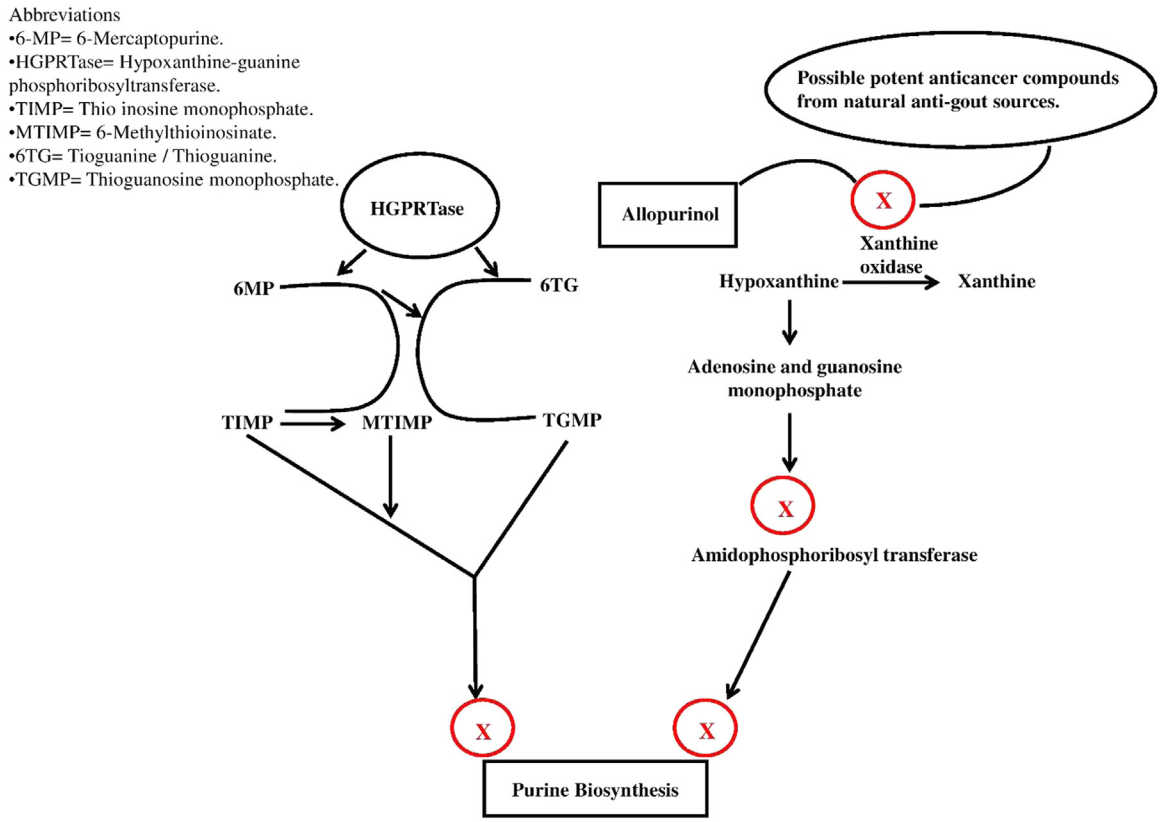

Fig.1. 6-MP and 6TG are transformed into TIMP and TGMP *in-vivo* with the help of HGPRTase enzyme, followed by further methylation of TIMP into MTIMP. TIMP, TGMP, and MTIMP are accumulated intracellularly and inhibit *de novo* purine biosynthesis. On the other side, Allopurinol and hypothetical natural anti-gout compounds inhibit XO enzyme that catalyzes the conversion of hypoxanthine to xanthine and xanthine cannot be converted to purine ribotides. Increased level of hypoxanthine causes production of adenosine and guanosine monophosphate that results in feedback inhibition of Amidophosphoribosyl transferase, a rate limiting enzyme of purine biosynthesis. The eventual result is the blockage of the *de novo* pathway of purine biosynthesis.

ity of XO by several flavonoids. Among them most notable candidates are apigenin (Ki=0.61μM), luteolin (Ki=1.9 μM), kaempferol (Ki=6.77 μM), rufigallic acid (100% inhibition by 1 mg), anthragallol (100% inhibition by 1 mg), chrycin ($IC_{50=}$2.5 μM), galangin ($IC_{50=}$4 μM), quercetin ($IC_{50=}$1.5 μM), myricetin ($IC_{50=}$1.5 μM), genistin (Ki=3.23 μM) and isovectin (Ki=5.22 μM) [34,53,54,56]. The flavonoids are naturally linked with sugar residues to increase the solubility, but bulky sugar groups reduce not only activity but also affinity towards XO [54,58]. From structure activity relationship studies, it was apprehended that the planar structure as well as C2=C3 bond on flavonoids facilitated the XO binding and inhibition while hydroxylation at ring B, C3 substitution or methylation was unfavorable for the activity [54,59].

4. Preclinical or clinical relevance of flavonoids for gout management

Flavonoids have been proved very potential molecules to manage hyperuricemia and gout in preclinical or clinical level [60,61]. Previously, quercetin and rutin from *Biota orientalis* extract elicited dose-dependent hypouricemic effect. In addition, significant inhibitory actions on xanthine dehydrogenase (XDH) or XO activities were found during *in vivo* animal study when orally administered to hyperuricemic mice at a dose of 100 mg/kg body weight. However, intraperitoneal administration at the same dose was not able to produce any observable effects. This was due to specific inhibition of XDH/XO in liver after oral administration rather than through other routes [62]. The flavonoids, luteolin and apigenin were evaluated for urate-lowering as well as liver XO inhibitory activities on oxonate-induced hyperuricemic mice. At a dose of 250 mg/kg body weight, the compounds significantly inhibit liver XO and showed remarkable anti-hyperuricemic along with anti-inflammatory properties therefore, they were proposed as promising agents for treating gouty arthritis [63]. A study was conducted on hyperuricemia mice to assess the effects of the five flavonoids genistein, apigenin, quercetin, rutin, and astilbin which showed a significant decrease in XO *in vivo* [64]. A particular reduction of uric acid formation was observed in hyperuricemic mice after oral administration of plant (Pistacia) extract rich in flavonoids like rutin, quercetin, kaempferol, and apigenin [65]. In a study, 15 flavonoids were selected to investigate their hypouricemic action in mice. Only quercetin, morin, myricetin, kaempferol, apigenin, and puerarin at 50 and 100 mg/kg body weight elicited hypouricemic action in hyperuricemic mice. These compounds significantly reduced serum urate level by inhibiting liver XO as well [66]. A Phase I clinical study certified quercetin, a well-known flavonoid molecule, as a safe drug because it did not show any toxicity even after chronic consumption (500 mg tablet) and therefore, recommended as a nutritional supplement for various ailments [60]. Recently, University of Pavia (Lombardy, Italy) has conducted a Phase IV clinical trial with nutraceutical (Uricemin) containing a combination of quercetin, rutin, bromelain and L-carnosine to evaluate its hypouricemic effect on patients with borderline uricemia. The results suggested a very promising outcome [67].

5. Cancer chemotherapeutic roles of comestible flavonoids

5.1. Apigenin (1)

Apigenin is a naturally occurring flavonoid found in various fruits, plants, and herbs that include orange, grapefruit, herbal tea chamomile, wheat sprout, and vegetables like parsley and onion [68]. It has been shown to possess anti-inflammatory and antioxidant properties [69]. It acts against XO; whose presence enables many medicinal plants to show mild to strong anti-inflammatory, anti-gout, and anti-arthritis activities [65]. It is mainly responsible for anti-hyperuricemic activity of *Olea europaea, Lychnophora trichocarpha* and *Pistacia integerrima* [63,65,70].

As the cytokines produced by fibroblast like synoviocytes are reported to be involved in joint destruction and inflammation, apigenin triggered apoptosis by activating stress activated extra cellular signal regulated kinase 1/2 (ERK1/2) pathway in the fibroblast like synoviocytes which has been experimented to be beneficial in rheumatoid arthritis [71]. Apigenin has been studied for its anticancer action on a wide variety of cancer cell lines *in vitro* as well as *in-vivo* animal models. Its anticancer activity on breast and prostate cancer was reported to be estrogen receptor (ER) mediated. Apigenin effectively suppressed the cell growth of DU-145 prostate and MDA-MB-231 breast cancer cells by the activation of caspase-3 which was modulated by ERβ. At higher ligand concentration, apigenin elicited higher transactivation through ERβ [72]. It also inhibited proteasomal chymotrypsin and induced apoptosis in breast adenocarcinoma cell lines [73]. Moreover, apigenin induced apoptosis in human epidermal growth factor receptor 2/neu (HER2/neu) over expressing breast cancer cells and has shown to effectively suppress Akt function by directly inhibiting phosphoinositide 3-kinase (P13K) activity [74,75]. Apigenin provided its antitumor activity on breast cancer by blocking phorbol 12-myristate 13-acetate (PMA)-mediated cell survival that was correlated with suppression of PMA-stimulated activator protein-1 (AP-1) activity [69]. It also inhibited cell proliferation and tumorigenesis of A2780 ovarian cancer cells by suppressing the expression of DNA binding protein inhibitor, ID1 through activating transcription factor 3 (ATF3) [76]. In addition, it caused cell cycle arrest at G2/M stage of A2780 cells. Apigenin inhibited the growth of pancreatic cancer cells through suppression of cyclin A and B along with the suppression of G2/M transition [46]. Moreover, it also inhibited human lung cancer angiogenesis by inhibiting hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) expression [76]. In A-549 cells and H1299 lung cancer cells, apigenin demonstrated TNF-related apoptosis-inducing ligand (TRAIL)-mediated tumor suppressing action through inhibiting the nuclear factor kappa B (NF-κB), Akt, and ERK signaling [77]. It effectively suppressed cellular migration, invasion, and metastasis via attenuated neural precursor cell expressed developmentally downregulated 9 (NEDD9)/non–receptor tyrosine kinases c-Src (Src)/Akt signaling in colorectal cancer cells [78]. Inhibition of the wingless-related integration site (Wnt)/β-catenin signaling was also found to be responsible for the anti-colorectal cancer activity of apigenin [79,80]. It abolished the human cervical cancer HeLa cells viability through induction of p53, Fas/apolipoprotein A1 (APO-1), and caspase-3 expression that facilitated G1 phase cell cycle arrest and apoptosis, respectively [81]. Apigenin caused diminished prostate cancer cell survival via downregulating the PI3K/Akt/NF-κB signaling [82]. Another anti-prostate cancer mechanism of apigenin included effective suppression of IκB kinase α (IKKα) and NF-κB [83]. Reversing of epithelial mesenchymal transition (EMT) and induction of G2/M phase cell cycle arrest were also found to be associated with anti-prostate cancer activity of apigenin [84]. Apigenin caused apoptosis in tongue oral cancer SCC-25 cells by suppressing cyclin D1 and E, inactivating cyclin dependent kinase 1 (CDK1), and inducing cell cycle arrest at G0/G1 and G2/M phases [85,86]. A comprehensive review on the anticancer mechanism of apigenin demonstrated that extrinsic apoptosis was mediated by enhancement of the mRNA expressions of caspase-3, -8, and TNF-α; and intrinsic apoptosis was mediated by cytochrome C, Bax, and caspase-3 induction [87]. Some of the other reported anticancer actions of apigenin include its potential activity against gastric, brain, liver, bone, leukemia, and skin cancers [88–93].

5.2. Chrysin (2)

Chrysin is a flavonoid which is mainly extracted from plants, honey, and propolis [94]. It possesses potent anti-inflammatory, and antioxidant properties [95]. Chrysin is the structural analogue of apigenin and possesses a strong XO inhibitory activity in a reversible competitive manner. Being the main constituent of honey, passiflora, propolis, and *Oroxylum indicum,* it plays a significant role in the remedy of gout [96].

Several studies demonstrated that chrysin is potent against cervical, esophageal squamous, breast, prostate, and colon carcinoma [44]. Chrysin derived from honey reduced cell proliferation and induced apoptosis in the PC-3 prostate cancer cells [97]. It was reported to inhibit angiogenesis with chymotrypsin and trypsin like proteasomal degradation [98,99]. It sensitized TNF-α induced cell death in human tumor cells through activation of caspase-8 and suppression of NF-κB and cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (C-FLIP)-L activation [100]. Chrysin was also reported to potentiate the cytotoxicity of anticancer drugs by depleting cellular glutathione [101]. It induced apoptosis in human leukemia U937 cells by the activation of caspase-3 that was associated with inactivation of Akt and X-linked inhibitor of apoptosis protein (XIAP) [102]. Chrysin was found to downregulate human telomerase reverse transcriptase (hTERT) expression in leukemia cells as well [103]. It caused G2/M cell cycle arrest through upregulation of p21 and downregulation of cyclin B1 in KYSE-510 human esophageal squamous carcinoma cells [104]. Moreover, it acted as a histone deacetylase-8 inhibitor and inhibited cell growth and differentiation in MDA-MB-231 breast cancer cells [105]. The MTT assay of chrysin demonstrated MCF-7 breast cancer cell proliferation inhibitory effect in a dose and time-mediated fashion [106]. It could inhibit cyclooxygenase-2 (COX-2) gene expression by targeting IL-6 in lipopolysaccharide (LPS)-stimulated macrophages, which provided a promising insight on the anti-inflammatory and anti-carcinogenic activity of chrysin [95]. Satisfactory effect of chrysin was observed against HeLa cervical cancer cells where it downregulated the proliferating cell nuclear antigen (PCNA) [107]. It was reported to obstruct the tumor formation in 7,12-dimethyl benz(a) anthracene (DMBA)-induced oral and skin carcinogenesis model by downregulating the phase-I enzymes, cytochrome 450 and cytochrome b5 and upregulating the phase-II enzymes like, glutathione S-transferase, glutathione, D-Tyr-tRNA deacylase and glutathione reductase [108,109]. The *in-vivo* anti-breast cancer activity of chrysin was also reported where modulation of phase I and phase II enzymes were associated [110]. It abolished the proliferation of colon cancer cells via suppressing the PCNA and growth factors, such as leptin and insulin like growth factor-1 (IGF-1) [111]. In human lung adenocarcinoma A-549 cells, chrysin upregulated caspase-3 and -9 and Bcl-2 Associated X-protein (Bax)/B-cell lymphoma 2 (Bcl-2) ratio to exert its anti-proliferative action [112]. The synergistic effect of chrysin and silibinin against T47D breast cancer cells was reported to be associated with the suppression of cyclin D1 and hTERT genes [113].

5.3. Kaempferol (3)

Kaempferol is a polyphenolic flavonoid also known as phytoestrogen, commonly found in vegetables, fruits, plants, and herbal medicines. It has health promoting properties that include anticancer, anti-inflammatory, and antioxidant properties [114,115]. Kaempferol inhibits XO by incorporating into its catalytic site, induces conformational changes and inhibits substrate binding [35,66,116,117]. A wide range of anti-gout medicinal plants, *e.g.*, *Pistacia integerrima, Petroselinum crispum, Erythrina strica, Tamus communis,* and *populus nigra* L. contain kaempferol as one of the active constituents [39,116]. Kaempferol reportedly has no significant effect on the uric acid level of normal rats but reduces SUA level in hyperuricemic rats [116].

It was found to be effective against breast, pancreatic, kidney, ovarian, lung, colon, prostate, cervical carcinoma, gliolblastoma, leukemia, bladder, and bone cancer [118–123]. By regulating CDK1, cyclin B, and p53, kaempferol inhibited cell proliferation in MCF-7 breast and HeLa cervical cancer cells [114]. Kaempferol is thought to function as a selective ER modulator and also functions as an inverse agonist for estrogen related receptors such as, ERα and ERγ by blocking their interaction with peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). It also suppressed the expression of estrogen related receptor (ERR) target gens pyruvate dehydrogenase kinase isoform (PDK)2 and PDK4 [124]. Kaempferol showed anti-proliferation activity on HCT-15 colon cancer cells which was comparable with the effects of doxorubicin and cisplatin [125]. In addition, kaempferol was reported to stimulate caspase-3 activity in HL-60 human leukemia cells [126,127]. In ovarian cancer cells, it decreased the expression of VEGF and inhibited angiogenesis by suppressing the ERK/NF-κB/c-myc/p21/VEGF pathway [128,129]. Moreover, kaempferol was reported to block the cell migration by transforming growth factor β_1 (TGF-β_1) induced EMT through recovering the loss of E-cadherin and suppressing the induction of mesenchymal markers in A-549 lung cancer cells. It also abolished TGF-β_1-induced Akt1 phosphorylation that was very essential for TGF-β_1-mediated induction of EMT and cell migration [130]. Through regulating Src kinase, MAPK, and COX-2, kaempferol also worked against melanoma [114]. It could reverse the vinblastine resistant phenotype by inhibiting P_{gp} activity in multidrug resistant human cervical carcinoma cells, KB-V1 [131]. The anti-brain cancer potential of kaempferol was also studied where it suppressed the growth and migration of glioma cells by downregulating oxidative stress, XIAP, ERK, and Akt; and at the time when kaempferol was loaded to mucoadhesive nano-emulsion or kaempferol-loaded nano-emulsion [120,132,133]. It attenuated hepatocellular carcinoma cells proliferation via suppressing microRNA 21 (miR-21), MAPK and HIF-1, enhancing phosphatase and tensin homolog (PTEN), downregulating PI3K/Akt/mammalian target of rapamycin (mTOR) signaling, facilitating the release of cytochrome C and causing loss to mitochondrial membrane potential (MMP) [134–136]. In the prostate cancer cells, kaempferol stimulated essential immune response via aggravating granulocyte-macrophage colony-stimulating factor (GM-CSF) production that later included phospholipase C (PLC), MAPK/ERK kinase 1/2 (MEK1/2), and protein kinase C (PKC) activation, that eventually caused dendritic cells aggregation to the tumor site [137]. The antiangiogenic activity of kaempferol was studied in OVCAR-3 and A2780/CP70 ovarian cancer cells where it abolished VEGF expression via both HIF-dependent and independent pathways [128]. In different oral cancer cells, kaempferol demonstrated proliferation inhibitory activity by causing cell cycle arrest at G0/G1 phase, suppressing Bcl-2, matrix metalloproteinase-2 (MMP-2), c-Jun, and hexokinase-2 expressions, activating epidermal growth factor receptor (EGFR), phosphorylating ERK1/2, upregulating Bax, and cleaving caspase-3, -9, and poly ADP ribose polymerase (PARP) [138–141].

5.4. Luteolin (4)

Being widely distributed in various edible plants, *i.e.*, carrot, pepper, celery, olive oil, peppermint, etc., luteolin is known for its cancer chemopreventive and chemotherapeutic potentials along with antioxidant, anti-inflammatory, antimicrobial, anti-allergic, cardio-protective and anti-diabetic activities [142]. It is reported, the anti-gout activity of luteolin is mainly due to the inhibition of XO [63,143,144]. The inhibition of NF-κB activation and reduced expression of cytokines including TNF-α, IL-1, IL-6, IL-8, COX-2, and inducible nitric oxide synthase (iNOS) are responsible for imparting the anti-inflammatory activity of luteolin [142].

The possible chemotherapeutic role of luteolin is mediated by the modulation of ROS levels, inhibition of topoisomerases I, II, NF-κB, and AP-1, upregulation of p53 and downregulation of P13K, STAT3, IGF1R, and HER2 [142]. It was previously reported, luteolin induced apoptosis by the activation of antioxidant enzymes, *i.e.*, superoxide dismutase and catalase in CH27 B cell lymphoma cells, which potentially played an important role in preventing the rebound activity of cancer cells [145–148]. It induced apoptosis in LNCaP human prostate adenocarcinoma cells via suppressing the intracellular prostate specific antigen (PSA) levels, and androgen receptor (AR) mRNA and protein expressions. Luteolin reduced the association between AR and heat shock protein-90 (HSP-90), causing AR degradation through a proteasome mediated pathway in a ligand-independent manner [149]. Involvement of suppressed miR-301 and VEGFR-2 expressions were also implicated in the anti-proliferative and anti-angiogenic activity of luteolin [150,151]. Synergistic anti-prostate cancer effect of luteolin was observed with gefitinib, epigallocatechin-3-gallate, and quercetin via inhibition of cyclin G-associated kinase (GAK), TGF-β, and C-Jun N-terminal kinase (JNK) [152–154]. In COLO205, HCT 116, and HeLa cells, it inhibited TNF-α induced NF-κB activation and downregulated the expression of A20 and cellular inhibitor of apoptosis protein-1 (C-IAP1) genes [155]. In azoxymethane incorporated colon carcinogenic cells, luteolin exhibited significant anti-proliferative activity via abrogating MMP-9 and -2, iNOS, COX-2, β-catenin, glycogen synthase kinase-3β (GSK-3β) and cyclin D1 [156–158]. Moreover, luteolin was reported for its apoptosis inducing properties in BIU-87, A-549, Huh-7, and non-small cell lung carcinoma (NSCLC) xenograft model [159–162]. A unique characteristic of luteolin has been proved in a study where it acted as a histone deacetylase inhibitor and promoted the action of cisplatin as a combinatorial therapy [163]. Moreover, *in-vivo* combinatorial treatment of luteolin and cyclophosphamide was seen to provide strong antioxidant defense mechanism with strong chemopreventive activity against mammary tumors [164]. In human HepG2, HLF, and HAK-1B liver cancer cells, luteolin downregulated STAT3 via two mechanisms; the ubiquitin-mediated breakdown in Tyr705 phosphorylated STAT3 and the systematic suppression in Ser727 phosphorylated STAT3 via CDK5 dysregulation, which in turn caused apoptosis through the Fas/CD95 upregulation [165]. Luteolin abolished the EGF-mediated action of EGFR signaling in MCF-7 and MDA-MB-231 human breast cancer cells where pathways like PI3K/Akt, MAPK/ERK1/2, and STAT3 were implicated to induce the anti-proliferative effect [166]. It could act against oral cancer via suppressed IL-6/STAT3 signaling, diminished CDKs, cyclins, and phosphor- retinoblastoma expressions, elevated caspase-9, -3 expressions, and enhanced cleaved PARP levels [167,168]. In head and neck squamous cell carcinoma, luteolin remarkably hindered tumor formation and growth via causing cell cycle arrest, attenuating cell migration, upregulat-

ing p53 mediated miR-195/215, let7C, and downregulating miR-135a [169]. In a number of liver cancer cells, luteolin exhibited anti-proliferative action and induced apoptosis through increasing Bax/Bcl-2 ratio, caspase-3, AMP-activated protein kinase (AMPK), TGFβ1, cyclin-dependent kinase inhibitor 1 ($p21^{WAF1}$)/CDK interacting protein (CIP)1, cyclin-dependent kinase inhibitor 1B ($p27^{KIP1}$), mothers against decapentaplegic homolog 4 (Smad4), Fas and p53 expressions, mediating PARP cleavage, causing cell cycle arrest at G1/S phase, and suppressing MMP, NF-κB, ERK1/2, and Akt activation [170–174]. A recent review on the anticancer action of luteolin has also mentioned its effect against skin, ovarian, glioblastoma, pancreatic, kidney, placental, and esophageal cancer [175].

5.5. Quercetin (5)

Quercetin is one of the most abundant bioflavonoids which are found in edible fruits and vegetables including onions, grapes, apples, tea, etc. [176]. It has been reported to be effective against allergy, inflammation, arteriosclerosis, and cancer due to its potent antioxidant and metal ion chelating capacity [176,177]. It is one of the most potent flavonoids which can interact with and modulate the activity of a variety of enzyme systems including lipooxygenase, COX, phosphodiesterase, and tyrosine kinase. Quercetin is a potent anti-gout compound exhibiting its activity through inhibition of XO enzyme as well as provides strong synergistic activity with kaempferol [39,116].

The proposed anticancer mechanism of action of quercetin is dependent on the inhibition of protein tyrosine kinase and inhibition of interaction of carcinogens with DNA [177]. It is reported to downregulate a number of tyrosine kinases including Abelson murine leukemia viral oncogene homolog 1 (ABL1), Aurora-A, -B, -C, dual specific protein kinase CLK1, fetal liver tyrosine kinase 3 (FLT3), Janus kinase 3 (JAK3), MET proto oncogene tyrosine kinase, NIMA related kinase (NEK) 4, NEK9, p21 (RAC1) activated kinase 3 (PAK3), PIM1 proto oncogene serine/threonine kinase, RET proto-oncogene tyrosine-protein kinase receptor, fibroblast growth factor receptor 2 (FGFR2), platelet-derived growth factor receptor (PDGF-R) α and β [178]. Quercetin suppressed CYP450 family of enzymes which had a significant role in the activation of a number of suspected human carcinogens [178,179]. It was reported to work against estrogen dependent breast cancer where suppression of the growth of MCF-7 cells took place via inhibition of the ER II expression [177]. In MCF-7 and MDA-MB-231 cells, quercetin also showed anti-proliferative activity via enhancing the miR-146a and caspase-3 expression [180]. In breast tumor-474 cells, quercetin mediated apoptosis via facilitating the increase in cleaved caspase-3, -8 and PARP levels, and suppressing STAT3, and MMP-9 [181]. Another study demonstrated that quercetin inhibited cell proliferation and induced apoptosis in HL-60 human leukemia cells by suppressing the expression of COX-2 and activating caspase-3 expression [182]. In a number of different human leukemia cells, quercetin exerted cancer suppressive effect through reducing the expression of cyclin A, D, E and D1, CDK-2 and -6, Rb phosphorylation, Notch 1, Akt, mTOR, Bcl2, MMP, causing cell cycle arrest at G1 phase, and enhancing the expression of caspase8, 9, and 3, p21 and p27 [183–186]. It inhibited AR expression at the transcriptional level and downregulated androgen inducible genes including human glandular kallikrein (hK2), ornithine decarboxylase gene (ODC), PSA, and NKX3.1, which were responsible in the progression and development of prostate cancer [187]. Quercetin was also reported to induce apoptosis in a number of cells like, SKOV-3 ovarian cancer cells and DLD-1 colorectal adenocarcinoma cells [188,189]. In caco-2 colon cancer cells, it exhibited anti-migration and anti-invasive properties by suppressing MMP-2, -9, TNF-α, COX-2, NF-κB expression, and IL-6 and upregulating the E-cadherin expression [190]. But fascinatingly, the anti-toll-like receptor 4 (TLR4) antibody was proposed to negatively influence the effectivity of quercetin. In colon 26 and colon 38 cells, quercetin abolished the viability of both cells and particularly mediated apoptosis in colon 26 cells via MAPK dependent pathway [191]. In hepatocellular carcinoma HepG2 cells, quercetin inhibited fatty acid synthase and enhanced p53 and Bax via reducing the levels of ROS, PKC, PI3K and COX-2 [192,193]. In A-549 human lung adenocarcinoma cancer cells, quercetin exerted apoptosis inducing property by upregulating the Bax and downregulating the Bc1-2 gene expression [194]. In JB6 Cl41 and A-549 cells, as an aurora B inhibitor, quercetin effectively abrogated lung cancer cells proliferation by suppressing the phosphorylation of histone 3 [195]. It mediated G2/M phase cell cycle arrest and thereby induced apoptosis in the 143B osteosarcoma cells as well [196]. Quercetin along with cisplatin controlled the proliferation of 143B osteosarcoma cells via enhancing the miR-217 and downregulating the Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (K-Ras) at both mRNA and protein levels [197]. In MG-63 osteosarcoma cells, quercetin mediated MMP loss, enhanced the levels of Bax, cytochrome C, caspase-9 and -3, and suppressed Bcl-2 expression [198]. The anti-brain cancer effect of quercetin was also evident where it abrogated the expression of phospholipase D1, NF-κB, COX-2, MMP-2, Hsp27, and p53, caused cell cycle arrest at G1 phase, and upregulated the levels of phosphatidic acid, mouse double minute 2 homolog (MDM2) mRNA, and caspase-3 [199–201]. Moreover, combination of resveratrol and quercetin was employed in HT-29 colorectal cancer cells which were able to reduce the expression of Sp1, 3, and 4 mRNA. These Specificity protein (Sp) transcription factors are believed to be overexpressed in colon and other cancers and regulate the genes required for cell proliferation and angiogenesis [202]. The combinatorial therapy of quercetin and trichostatin A was observed to exhibit better anticancer activity against HL-60 cells than quercetin or trichostatin A alone [179]. In PC3 and DU-145 prostate cancer cells, quercetin and curcumin combined demonstrated significant promise by suppressing DNA methyl transferase, facilitating global hypomethylation, revitalizing the level of AR mRNA and protein and mediating apoptosis through depolarization of mitochondria [203]. Using LNCaP and PC-3 cells, the combined effect of quercetin with 2-methoxyestradiol on the anti-proliferation of prostate cancer is also well documented [204]. Combination of (−)-epigallocatechin gallate, quercetin and docetaxel caused mentionable cell cycle arrest at G2/M phase and induced apoptosis by suppressing the PI3K/Akt and STAT3 pathways in LAPC-4-AI and PC-3 prostate cancer cells [205]. A review on the anticancer properties of quercentin has also mentioned its capacity to limit a number of other cancers like kidney, thyroid, skin, cervical, head and neck, gastric, eye and bladder cancer [206].

5.6. Rutin (6)

Rutin is a well-known glycoside dietary flavonoid, largely found in buckwheat, amaranth, asparagus, citrus fruits, and berries such as *Ruta graveolens* (common rue) and *Morus alba* (mulberry) [207,208]. It is reportedly responsible for the bioactivity of many natural products which include anticancer, anti-gout, anti-inflammatory, antioxidant, anti-hypertensive, antidepressant, antidiabetic, antiaging, and antimicrobial properties [209–212]. It is a quercetin derivative chemically known as quercetin-3-rhamnoglucoside [213,214]. As a phyto-constituent, rutin is reported to inhibit the XO enzymatic activity, which is suggestive of its anti-gout property [64,213,215].

Rutin is also documented as a chemotherapeutic and chemopreventive agent, as it inhibits the formation of ROS; induces su-

per oxide dismutase, catalase, and glutathione peroxidase; caspase-3 mediated apoptosis; inhibits NF-κB and associated cytokines, and suppresses the migration and adhesion of malignant cells [216,217]. Rutin demonstrated significant anti-skin carcinogenic effect in DMBA and croton oil-induced swiss albino mice by alleviating the oxidative stress through enhancing the levels of endogenous antioxidant enzymes [210]. In 786-O renal carcinoma cells, rutin remarkably reduced cell viability via causing a notable rise in the sub-G1 population of carcinoma cells [218]. Treatment of rutin in human leukemia HL-60 cells demonstrated its tumor growth suppressing effect [219]. In HCT-116 human colon cancer cells, rutin abrogated cell migration, caused cell cycle arrest at G0–G1 phase, and activated caspase-3 and β-actin to mediate its anti-invasive effect [220]. In the enrichment analysis of rutin in human colon cancer SW480 cells using miRNAs-lncRNAs-mRNAs-TFs network, it induced cell cycle arrest at sub-G1 phase, and reduced cell population and metabolism via depleting glucose, lipid, and protein metabolism, regulating endoplasmic reticulum stress responses, and mediating both extrinsic and intrinsic apoptosis [221]. Rutin and silibinin in combination demonstrated anti-colon cancer activity in HT-29 cells through modulating the genes associated with apoptosis, inflammation, and MAPK mediated pathway [222]. In *in vitro,* rutin-chitosan nano-conjugates showed significant cell cycle arrest at the S phase followed by induction of apoptosis in triple negative breast cancer cells [223]. In MDA-MB-231 breast cancer cells, intraperitoneal injection of rutin notably hindered the malignant cell growth and proliferation [224]. Rutin restored chemosensitivity to cyclophosphamide in human breast cancer cells via causing cell cycle at G2/M and G0/G1 phases and inhibiting the P-glycoprotein and breast cancer resistance protein activity [225]. Rutin and orlistat in combination demonstrated tumor suppressing effect in MCF-7 breast and PANC-1 pancreatic cancer cells by alleviating tumor volume, carcinoembryonic antigen, cholesterol, fatty acid synthase and malondialdehyde and enhancing glutathione level [217]. Rutin exerted satisfactory action against neuroblastoma through mediating G2/M cell cycle arrest, reducing the Bcl-2, and TNF-α expression and Bcl-2/Bax ratio and thereby inducing apoptosis [226]. In human lung A-549 and colon HT-29 and Caco-2 cancer cells, rutin notably disturbed the cancer cells' viability by suppressing their adhesion and migration in A-549 and HT-29 cells, and particularly reducing the superoxide production in HT-29 cells [216]. In combination with oxidovanadium, rutin improved the anticancer effect in A-549 cells via scavenging the ROS and inducing the endogenous antioxidants [227]. Rutin treatment in human cervical cancer C33A cells disrupted the cell viability, increased ROS level and mediated apoptosis via provoking cell cycle arrest at G0/G1 phase, causing reduction in MMP and activating caspase-3 [228]. Newly developed rutin nanoemulsion showed notable ROS induction in human prostate cancer PC3 cells which in turn induced apoptosis in the cancerous cells [229]. Rutin demonstrated synergistic effect with 5-fluorouracil through the induction of p53 mediated apoptosis and downregulation of Bcl-2 protein on prostate cancer cells [214]. Several comprehensive reviews on the molecular mechanisms of the anticancer action of rutin stated the involvement of pathways like Wnt/β-catenin, p53-independent pathway, PI3K/Akt, JAK/STAT, MAPK, p53, TNF-α, ILs, light chain 3/Beclin, Bcl-2, VEGF, and NF-κB [230–232].

5.7. Baicalin (7)

Baicalin (5, 6-dihydroxy-7-O-glucuronide flavone) is a flavonoid isolated from the roots of Chinese medicinal plant *Scutellaria baicalensis* [233]. It is reported for its anti-oxidative, anti-inflammatory, anti-HIV, and anti-proliferative activities [234–236]. Baicalin is reported for its XO inhibitory activity and therefore beneficial in the prevention and treatment of hyperuricemia and gout [237].

The tumor suppressing properties of baicalin include its capacity to limit free radical generation, suppress NF-κB, COX-2, and several gene activations, which are vital for controlling cell cycle [238]. Baicalin disrupted invasive action of MDA-MB-231 breast cancer cells via suppressing the MMP-2, -9, urokinase-type plasminogen activator (uPA), and uPAR expressions by further regulating the p38 MAPK signaling [239]. Baicalin nanocapsules formulation exhibited significant cancer suppressing effect up to 216 times in MCF-7 and 31 times in MDA-MB-231 cells, mainly via inducing apoptosis with notable enhancement of p53 expression [240]. It promoted apoptosis in MCF-7 cells via mediating cell cycle arrest at G_0/G_1 phase and enhancing the levels of p53 and Bax [241]. Baicalin suppressed the metastasis in MDA-MB-231 cells by reversing the EMT, that was induced via suppression of expression of β-catenin, a cell-cell adhesion and gene transcription coordinator [242]. In SMMC-7721 human hepatocellular carcinoma cells, baicalin induced apoptosis and autophagy by suppressing the expression level of CD147 [243]. Baicalin in combination with hyperthermia enhanced the anti-apoptotic property of hyperthermia in U-937 myelomonocytic leukemia cells by dephosphorylating Akt, enhancing the levels of caspase-3 activation, ROS, JNK and p38, and decreasing MMP, and antioxidant enzyme levels [244]. In CA46 Burkitt lymphoma cells, baicalin exerted anti-proliferative action by facilitating DNA fragmentation, and intrinsic mitochondrial cell death pathway, as evidenced by elevated cleaved levels of caspase-3, -9, and PARP and downregulated PI3K/serine/Akt signaling [245]. Baicalin demonstrated significant cytotoxicity in HL-60 human leukemia cells via increasing the levels of Gadd153, Bax, cytochrome C and caspase-3 and -12, ROS, Ca^{2+} and reducing MMP, Grp78 and Bcl-2 [246]. In L1210 mouse leukemia cells, Antoksyd S and baicalin exerted antioxidant and apoptosis inducing effects *in vitro* [247]. In the leukocytes of children with acute lymphocytic leukemia, baicalin mediated apoptosis in the cancerous cells, but not in the healthy cells [248]. Baicalin and wogonoside in combination with glycoside hydrolase exerted promising anticancer properties against human colorectal and breast cancer cells via causing cell cycle arrest at S phase and therein mediating apoptosis [249]. In HT-29 human colon cancer cells, baicalin mediated apoptosis via repressing the c-myc, miR-10a, miR-23a, miR-30c, miR-31, miR-151a and miR-205 expressions [250]. Baicalin along with its oxidovanadium (IV) complex disrupted the viability of A-549 human lung cancer cells through facilitating ROS generation [251]. TRAIL and baicalin in combination was able to mediate apoptosis in A549 and H2009 cells through activating p38 MAPK and aggregating ROS [252]. Akt /mTOR mediated pathway was also proposed to be implicated in the anti-lung cancer potential of baicalin in H1299 and H1650 cells [253]. Baicalin encapsulated nano-micelles formulation demonstrated better cytotoxicity in A-549 cells through inducing apoptosis [254]. In A-549 and mouse lewis lung cancer cells, baicalin showed anticancer effect by enhancing the antioxidant enzyme superoxide dismutase and downregulating HIF-1α [255]. In mucoepidermoid carcinoma Mc3 cells, baicalin caused aggregation of cells at the G_0/G_1 and G_2/M phase along with a subsequent reduction in the number of cells at S phase [256]. In addition, it mediated apoptosis in Mc3 cells that was evidenced by DNA fragmentation, nuclear condensation, and further fall in the MMP. The proliferation inhibitory effect of baicalin was investigated in OVCAR-3 and A2780/CP-70 ovarian cancer cells and IOSE-364 normal ovarian cells. Baicalin successfully and selectively inhibited the viability of ovarian cancer cells via suppressing the expressions of cancer promoting genes such as, VEGF, HIF-1α, c-myc, and NF-κB [257]. Baicalin has also been illustrated as the

first flavonoid based lysine-specific demethylase 1 (LSD1) inhibitor [258]. LSD1 has been reported to be overexpressed in many malignant tumors, including breast, colon, prostate, lung, gastric cancers, and others [259]. Baicalin has been proven to induce direct antitumor activity on a number of human prostate cancer cells including DU145, PC-3, LNCaP, and CA-HPV-10 [260]. This antitumor action of baicalin is accompanied by promotion of apoptosis, which is further evidenced by cellular nucleus fragmentation, DNA fragmentation, activation of caspase-3, breakdown of PARP, and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL). Baicalein was also studied against HeLa cervical cancer cells. It restricted the HeLa cells proliferation via induction of apoptosis through a caspase-3-dependent pathway [261]. This apoptotic pathway is also guided by the suppression of Bcl-2 and enhancement of Bax, Fas, Fas ligand and caspase-8. Baicalin inhibited the cancerous potentials of U87 and U251 human glioblastoma cells through causing rise to the intercellular Ca^{2+}, loss of MMP, and maturation of microtubule-associated protein 1A/1B-LC3B as evidenced by the initiation of autophagy via PI3K/Akt/mTOR pathway [262]. Several comprehensive reviews on the anticancer potentials of baicalin have mentioned mechanisms like mediation of apoptosis, autophagy and cell cycle arrest, suppression of angiogenesis, metastasis, and regulation of the immune response and several molecular targets are involved [263,264]. In addition, the main molecular targets of baicalin against cancer included PI3K/Akt/mTOR, NF-κB, MAPK/ERK, and Wnt/β-catenin [264]. Some other reported anti-proliferative actions of baicalin include its effect against osteosarcoma, bladder, hepatoblastoma, mucoepidermoid, skin, colorectal, cervical, and triple negative breast cancer [265–275].

5.8. Baicalein (8)

Baicalein (5,6,7-trihydroxyflavone) is a bioactive flavone which was isolated and identified from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora* [276]. In fact, it is the aglycone part of baicalin [277]. Baicalein has been found to exhibit numerous pharmacological actions such as antioxidant, anti-inflammatory, anticancer, antiviral, anti-ulcerative colitis, and neuroprotective activities [278–281]. Baicalein was reported for its XO inhibiting properties that contribute to manage hyperuricemia and gout, and demonstrated a synergistic effect when combined with allopurinol [237]. Here, baicalein attached itself with XO which was mediated through hydrophobic interactions and hydrogen bonds, resulting in a more compact shape of XO.

Baicalein induced apoptosis in T24 bladder cancer cells through the loss of mitochondrial transmembrane potential ($\Delta\Psi$m), G1/S cell cycle arrest, release of cytochrome C, activation of caspase-9 and -3, and obstructing Akt phosphorylation [282]. In 5,637 bladder cancer cells, baicalein mediated apoptosis in ROS-regulated upregulation of caspase pathway [283]. It was also reported that baicalein induced apoptosis and inhibition of proliferation in bladder cancer cells through an opposite action of p38 MAPK and Akt and inhibition of cyclin-dependent protein kinase 1 (CDC2)-survivin pathway [284]. Baicalein exhibited apoptotic outcome in FRO anaplastic thyroid cancer cells via modulation of the MAPK and Akt pathway related protein expressions [285]. Inhibition of activation of the Akt/NF-κB and STAT3 signaling were reported to be implicated in the anticancer effect of baicalein on cholangiocarcinoma [286]. Downregulation of Bcl-XL and myeloid cell leukemia 1 (Mcl-1) and upregulation of Bax and Bad were shown to be mainly associated with the effect of baicalein against nasopharyngeal carcinoma [287]. Baicalein, as 12-lipoxygenase inhibitor, demonstrated intrinsic apoptosis and cell cycle arrest at the G0/G1 phase of cell cycle in human prostate DU-145 and PC-3 cell lines [288]. The associated mechanisms were reduced levels of survivin and Akt phosphorylation, activation of caspase-3 and -7, reduced Bcl-2 and Bcl-XL expression in DU-145 cells, and an alteration in Bcl-2/Bax levels in PC-3 cells. Autophagy mediated cell death in prostate cancer cells by baicalein was reported where it activated the AMPK/ Unc-51 like autophagy activating kinase 1 (ULK1) pathway and abolished the expression of anti-autophagy molecules of mTOR/raptor complex 1 [289]. Baicalein was documented to abolish the MMP-2 expression in ovarian cancer cells through a p38 MAPK-mediated NF-κB pathway [290]. Moreover, baicalein induced apoptosis in various other human cancers such as pancreatic cancer cells HPAC, pancreatic neuroendocrine tumor cells BON1, NSCLC H460 cells, and lung squamous carcinoma CH27 cells [291–295]. A study argued that the anticancer potentials of baicalein were largely because of autophagy, rather than apoptosis, that took place through AMPK/ULK1 pathway upregulation and mTOR/Raptor complex 1 inhibition [289]. In MCF-7 and MDA-MB-231 breast cancer cells, baicalein promoted autophagy and apoptosis by downregulating the PI3K/Akt signaling [296]. In MDA-MB-231 cells, baicalein caused apoptosis via the production of Ca^{2+}, inhibition of Bcl-2, elevated levels of Bax and caspase-3, decreased levels of $\Delta\Psi$m, and promotion of cytochrome C release [297]. In a mouse model of breast cancer, inhibition of tumor generation by baicalein was associated with elevated DNA-damage-inducible transcript 4 (DDIT4) expressions, that in turn caused mTOR and growth inhibition [298]. Baicalein abolished EMT and suppressed both special AT-rich sequence-binding protein-1 (SATB1) and Wnt/β-catenin to exert its anti-metastatic effect on MDA-MB-231 cells [299]. A combination of baicalin and baicalein treatment demonstrated a synergistic effect on inducing apoptosis in MCF-7 cells by activating caspase-3 and -9, reducing Bcl-2, and enhancing Bax or p53 expression through the ERK/p38 MAPK pathway [300]. Baicalein mediated apoptosis in RPMI8226 human myeloma cells through inducing cell cycle arrest at G_0/G_1 phase, and reducing the 12-lipoxygenase expression [301]. It showed anticancer activity in H22, Bel-7404, and HepG2 hepatocellular carcinoma cells where regulation of cyclin D1 transcription through a β-catenin-mediated pathway, eventually promoting cell cycle arrest at G0/ G1 phase and disturbed cell proliferation [302]. Baicalein suppressed the mRNA and protein expressions of CD24 to exert it action against hepatocellular carcinoma [303]. Baicalein, along with luteolin has been demonstrated to cause apoptosis in LoVo colorectal adenocarcinoma cells via activation of caspase 3 and decreased expression of PCNA [304]. It caused apoptosis in HCT-116 human colorectal cancer cells as well via S phase cell cycle arrest and caspase mediated mechanism [305]. Baicalein caused both autophagy and apoptosis in U251 glioma cells through activating the phosphorylation of AMPK [306]. In HeLa cervical cancer cells, baicalein caused apoptosis through the mitochondrial and the death receptor pathways [261]. Baicalein caused cell cycle arrest at G_0/G_1 phase through suppression of cyclin D1 via the Akt–GSK3β signaling to abolish the proliferation of SiHa and HeLa cervical cancer cells [307]. A review encompassed combined anticancer activities of baicalein, wogonin, and baicalin, where tumor suppressing actions were exhibited in number of ways including induction of apoptosis and cell cycle arrest, NF-κB inhibition, ROS scavenging, and even pro-oxidative remarks in some cases [238]. Another review on the cancer suppressing property of baicalein has mentioned about its anti-metastatic, anti-angiogenic, and anti-inflammatory actions [308]. In case of a number of hematological malignancies, *i.e.*, leukemia, lymphoma, myeloma, a review accumulated mechanisms like, inhibition of growth signal, protein tyrosine kinase, phosphorylation of IkB-alpha, β-catenin, c-myc, cyclin D1, integrin β7, 12-lipoxygenase, ABCG2 (TP Binding Cassette Subfamily G Member 2), and Bcl-XL; suppression of mRNA expression

of PDGF-A, IL-6, and XIAP; cleavage of PARP, JAK, STAT3, MAPK, Akt, and ERK1/2 phosphorylation; upregulation of Fas, caspase-3, -8 and -9, ROS-mediated mitochondrial dysfunction pathway; and downregulation of anti-apoptotic and upregulation of apoptotic components of PI3K/Akt pathway, which were holistically involved in the anti-leukemic activity of baicalein [309]. Another review mentioned the role of suppressed levels of mTOR and MMP-2 and -9 in the tumor regulatory effects of baiclein, in addition to the previously mentioned proteins [279]. Baicalein and baicalin in combination abolished angiogenesis and have shown to inhibit a number of cancers including ovarian, liver, breast and bladder via abrogating the expressions of VEGF, HIF-1α, c-myc, NF-κB, STAT-3, programmed death-ligand 1 (PD-L1), interferon-γ, Bcl-2 and activating the expressions of caspase-3 and -9, Bax, p53 mainly through following ERK/p38 MAPK signaling [235,257,300,310,311]. Baicalein in combination with paclitaxel produced synergistic effect in A-549/paclitaxel drug-resistant human lung cancer xenografts and ameliorated the multidrug resistance of paclitaxel [312]. Combinatorial effect of baiclein and Docetaxel against thyroid cancer was recently reported [313]. Baicalein was also reported in some other studies, where its effectivity against gastric, lung, ovarian, colorectal, liver, prostate, skin and bone cancer were evident [290,314–322].

5.9. Galangin (9)

Galangin (3,5,7-trihydroxyflavone) is a flavonoid that is found in high concentrations in *Alpinia officinarum, A. galanga,* and *Helichrysum aureonitens*, popular medicinal plants of Asia and Africa, respectively [323–325]. Galangin exerts many pharmacological properties including anti-inflammatory, antiviral, antibacterial, antifungal, and antidiabetic activities [326–328]. Galangin was found to considerably inhibit XO activity with the inhibition of superoxide radical (O_2^-) generation [329]. This inhibition of O_2^- radical generation is suggested to be due to the competitive inhibition of uric acid formation followed by a Ping-Pong mechanism.

Galangin reduced cell proliferation and induced apoptosis in HCT-15 and HT-29 colon cancer cells via activation of caspase-3/-9 and the release of apoptosis inducing factor (AIF) from the mitochondria into the cytosol [330]. Moreover, galangin-treated human colon cancer cells demonstrated alteration in the MMP and mitochondrial dysfunction to exert its chemotherapeutic effect. Induction of cell cycle arrest at the G2/M or G1 phase was also implicated to be involved in the anti-proliferative role of galangin in HCT-116 cells [331]. Galangin also induced apoptosis in human head and neck squamous cell carcinoma, gastric cancer SNU-484 cells, human colon cancer cells, and B16F10 melanoma cells via caspase dependent mitochondrial pathway [332–334]. Another study demonstrated that galangin induced autophagy and apoptosis in HepG2 cells by mediating the phosphorylation of AMPK and liver kinase B1 (LKB1), thereby suppressing the activity of mTOR and Akt [335]. Functionalized selenium nanoparticles formulation with galangin mediated fall in MMP, activation of caspase-3, and translocation of phosphatidylserine via following a ROS-dependent Akt and p38 signaling to ameliorate cancer in HepG2 cells [336]. Galangin treatment in MHCC97H hepatocellular carcinoma cells caused downregulation of H19 and miR675, which in turn mediated better p53 expression to ultimately facilitate apoptosis [337]. A study showed that galangin inhibited angiogenesis in ovarian cancer cells by modulating Akt/70-kDa ribosomal protein S6 kinase (p^{70S6K})/HIF-1α/VEGF pathway [338]. A similar p53 dependent anti-ovarian cancer effect of galagin was recently reported following quite identical mechanistic pathway [339]. In SKOV3 ovarian cancer cells, galangin with gold nanoparticles mediated apoptosis via upregulating the p53, and caspase-8 expressions [340]. Moreover, Galangin suppressed the invasion and migration in renal cell carcinoma cells through inhibiting the EMT and inducing apoptosis [341]. Also, galangin was reported to prevent the metastasis of osteosarcoma by inhibiting the PI3K/Akt/MMP-2/-9 signaling pathway [342]. Galangin produced anti-angiogenic action in glioma cells via downregulating the expression of CD44, EMT, and VEGF [343]. Galangin treatment with chloroquine promoted apoptosis in U87MG and U251 glioblastoma cells via causing DNA damage, and upregulating the expression of Bax and cleaved PARP-1 [344]. In human glioblastoma cells, galangin suppressed the S-phase kinase associated protein 2 (Skp2) mediated EMT, and therein provided anti-proliferative effects [345]. The anti-brain cancer effect was also accompanied by decreased disintegrin and metalloproteinase domain-containing protein 9 (ADAM9) expression and ERK1/2 activation [346]. It exhibited chemopreventive action in HeLa cells through causing increased levels of ROS and carbonyl stress, and inhibition of glyoxalase-1 and nuclear factor erythroid 2-related factor 2 (Nrf2) [347]. The apoptosis inducing effect of galangin in A498 renal cancer cells was accompanied by elevated expressions of Bax, cytochrome C, reduced expressions of Bcl-2 and PI3K/Akt/mTOR pathway [348]. It ameliorated human laryngeal cancer through mediating apoptosis and autophagy, that were guided via suppression of p38 and Akt/NF-κB/mTOR signaling [349]. Galangin worked against cholangiocarcinoma via repressing the miR-21 expression [350]. Galangin mediated apoptosis in nasopharyngeal carcinoma via causing S-phase cell cycle arrest through abolishing the PI3K/Akt pathway [351]. It exhibited anti-skin carcinogenesis activity *in -vivo* and in B16F10 melanoma cells via remarkable inhibitory action on tyrosinase [352]. In benzo(a)pyrene-induced stomach carcinogenesis, galangin mediated chemopreventive effect via downregulating the expression of aryl hydrocarbon receptor (AhR), aryl hydrocarbon receptor nuclear translocator (ARNT), and cytochrome P1A1 [353]. Galangin promoted TRAIL-mediated apoptosis in human breast cancer cells via following the TRAIL/caspase-3/AMPK signaling [354]. A review on the apoptotic and autophagic mechanism of galangin against hepatocellular carcinoma worked on several ways like Warburg effect reversal, cell cycle arrest at G0/G1 phase, generation of ROS, endoplasmic reticulum mediated stress, mitochondrial-dependent apoptotic pathway, and abolishing of metastasis, angiogenesis and multidrug resistance [355]. Galangin and myricetin attenuated the VEGF release via following the Akt/p^{70S6K}/HIF-1α pathway in A2780/CP70 and OVCAR-3 cells angiogenesis [338]. Galangin with berberine combination exerted synergistic effect in esophageal carcinoma through causing cell cycle arrest at G2/M phase, increasing the ROS levels, and downregulating the Wnt3a and β-catenin expressions [356]. In human fibrosarcoma HT-1080 cells, galangin and kaempferol abolished the phorbol-12-myristate-13-acetate-mediated expression of MMP-9 through abrogating the NF-κB and AP-1 activations [357]. Galangin and TNF in combination synergistically produced anti-breast cancer effect via causing DNA fragmentation, upregulating the caspase-3, 8, 9 and Bax and downregulating the Bcl-2 expressions [358]. Galangin in combination with TRAIL demonstrated good anti-lung cancer effect in A-549 cells [359]. Galangin loaded with polyethylene glycol modification of liposomes exhibited considerable cytotoxicity against hepatoma cells through inducing apoptosis [360]. Galangin, as a hydrophobic drug, being loaded into niosomes showed considerable fall in mini-chromosome maintenance 3 (MCM3) immunostaining hepatocytes and neoplastic hepatic injury with less hepatic adenomas, which was suggestive of its promising effect against hepatocellular carcinoma [361].

5.10. Myricetin (10)

Myricetin (3,5,7,3′,4′,5′-hexahydroxyflavone) is a flavonoid which is found in common dietary sources including vegetables, fruits, nuts, berries, tea, red wine, and in medicinal herb *Azadirachta indica* [362–365]. The compound shows a wide range of biological activities including anti-oxidant, antidiabetic, and anti-inflammatory activities [366]. Myricetin is reported for its XO inhibitory activity that suppressed oxidative injury by ischemic-reperfusion and found to be effective in preventing gout [367]. Moreover, the dual inhibitory role of myricetin on XO and COX-2 is also reported [368].

Myricetin inhibited cell proliferation and promoted apoptosis in many cancer cell types including liver, pancreatic, lung, and colon cancer cells [369–371].In HT-29 colon cancer cells, myricetin performed as a human flap endonuclease 1 (hFEN1) inhibitor that can preferentially be used in targeted anticancer therapy [372]. It demonstrated significant anti-metastatic, pro-apoptotic, and cytotoxic activity in prostate cancer cells by inhibiting pro-viral integration site for Moloney murine leukemia virus-1 (PIM1), a Ser/Thr protein kinase in the PIM family, and suppressing the PIM1/CXC-chemokine receptor 4 (CXCR4) interactions [371]. It showed anti-invasive property on human glioblastoma cells through abolishing the ERK-dependent COX-2/Prostaglandin E_2 activation and MMP-9 activity [373]. The encapsulation of myricetin into nano-sized mixed micelle demonstrated improved cytotoxicity in DB-TRG glioblastoma cells through following the mitochondrial apoptotic pathway [374]. It showed anti-proliferative action in U251 human glioma cells via causing mitochondrial-induced cell death, cell cycle arrest at G2/M phase, generation of ROS, and suppression of cell migrations [375]. Myricetin-loaded micelles exhibited better anti-glioblastoma effects than free myricetin, where it mediated changes in the apoptotic proteins Bcl-2, Bcl-2 associated agonist of cell death (BAD), and Bax expressions [376]. In A-549 cells, myricetin showed anti-invasive property via suppressing the ERK1/2 signaling [377]. Moreover, myricetin was capable of inhibiting the invasive migration of radiotherapy resistant lung cancer cells A549-IR via reducing the MMP-2 and -9 expressions through inhibiting the focal adhesion kinase (FAK)-ERK signaling [369]. It again acted against A-549 cells via mediating sub-G1 and S phase cell cycle arrest and ROS–mediated mitochondrial cell death pathway [378]. The downregulation of MMP-2 and -9 expressions were also observed in myricetin treated T24 bladder cancer and MDA-MB-231 breast cancer cells [379–381]. It worked as a chemopreventive agent as well by suppressing breast tumor growth via decreasing VEGF, VEGFR2 and p38 MAPK expressions [382]. Gold nanoparticles in combination with myricetin showed promising anti-breast cancer potential where the combination downregulated the MMP and caused increased generation of ROS [383]. In HCT-15 cells, myricetin decreased cell proliferation and mediated apoptosis via promoting mitochondrial dysfunction and the Bax/Bcl-2 pathway [370]. It also showed pro-apoptotic effect on EC9706 and KYSE30 esophageal cancer cells via modulating the mitotic arrest deficient 1-like protein 1 (MAD1) and ribosomal S6 kinase 2 expressions [366]. Myricetin performed as a chemopreventive agent against skin cancer via suppressing Fyn kinase activity [384]. It ameliorated skin cancer angiogenesis in mice by abrogating the PI3K activity and Akt/p^{70S6K} phosphorylation [385]. It demonstrated antiangiogenic activity in human umbilical vascular endothelial cells (HUVECs) via mediating ROS-generated apoptosis and suppressing PI3K/Akt/mTOR pathway [386]. The anti-skin carcinogenic effect of myricetin was also guided through multiple proteins like, JAK1, proto-oncogene c-RAF, MEK1, mitogen-activated protein kinase kinase 4 (MKK4), and Fyn [387]. Anticancer activity against A431 human skin cancer cells by myricetin was because of ROS-mediated changes in MMP, alteration in expressions of Bax, Bcl-2, and thereby initiation of apoptosis [388]. Myricetin bulk and nano-forms exhibited anticancer action in myeloma patients through causing a rise in p53 expressions and ROS levels [389]. Myricetin along with mythyl eugenol demonstrated anti-proliferative effect on HeLa cells by causing G0/G1 phase cell cycle arrest, $\Lambda\Psi m$ loss and increased caspase-3 levels [390]. In MCF-7 cells, myricetin demonstrated a new mechanism of repressing the telomeric G-quadruplex structure to exert its anticancer action [391]. A comprehensive signaling cascade PAK1/MEK/ERK/GSK-3β/β-catenin/cyclin D1/PCNA/survivin/Bax-caspase-3 was found to be involved the anti-breast cancer effect of myricetin in MCF-7 cells [392]. The effect of myricetin on triple negative breast cancer cells was proposed to be because of autoxidized myricetin mediated oxidative stress, that eventually caused ROS production through Fenton reaction [393]. In MDA-MBA-231 cells, it effectively abrogated the expression of MMP-2/9 and mRNA levels of *ST6GALNAC5* to produce its anti-invasive effect [379]. The anti-breast cancer drug docetaxel became much more sensitized to myricetin when given via lipid nanoparticles to produce better effect in MDA-MBA-231 cells [394]. Myricetin exhibited anti-proliferative effect in cisplatin-resistant OVCAR-3 and A2780/CP70 cells through Bcl-2 and p53-mediated pathway [395]. In SKOV3 cells, it caused double strand breaks to DNA and stress in endoplasmic reticulum, that in turn led to apoptotic cell death [396]. It exerted effective response in SNU-790 human papillary thyroid cancer cells via causing DNA condensation, caspase activation, Bax:Bcl-2 ratio enhancement, released of AIF, and changes in MMP [397]. Myricetin produced anti-thyroid cancer effect on SNU-80 cells via inducing sub-G_1 phase cell cycle arrest, DNA condensation, release of AIF, and activation of caspase and Bax:Bcl-2 ratio [398]. It provided promising effect against hepatocellular carcinoma through abrogating the PAK1 expression, that was coordinated via suppression of several pathways like MAPK/ERK, PI3K/Akt, and Wnt/β-catenin signaling [399]. Another mechanistic pathway, Akt/p70s6k1/BAD was also proposed to be implicated in the mitochondria-mediated apoptotic action of myricetin in HepG2 cells [400]. Myricetin mediated cytotoxic effect in hepatocellular carcinoma cells via causing rise to ROS levels, swelling of mitochondria, MMP loss, release of cytochrome C, and caspase-3 activation [401]. It showed anti-proliferative property in HepG2 and Huh-7 cells, where suppression of yes associated protein (YAP) guided the stimulation of large tumor suppressor kinase 1/2 (LATS1/2) activation [402]. The anti-leukemic effect of myricetin was also found to be prominent in K562 cells where it interfered in the purine nucleotides biosynthesis via abolishing the human inosine 5′-monophosphate dehydrogenase (*h*IMPDH1/2) catalytic activity [403]. In HGC-27 and SGC7901 gastric cancer cells, myricetin being bound to ribosomal S6 kinase 2 (RSK2), caused elevated MAD1 expression, which eventually mediated anti-proliferative effect [404]. A review on the anti-cancer action of myricetin has mentioned about its interaction with a number of onco-proteins including Akt, Fyn, MEK1, and JAK1–STAT3 to abrogate the neoplastic pathway in invasive cells [405]. Moreover, according to the review, myricetin acted as an antimitotic agent in liver cancer via focusing on the CDK1 overexpression. Recent reviews have also accumulated the comprehensive activities of myricetin on various cancer cell deaths, proliferation, angiogenesis, metastasis and their cellular signaling mechanisms to induce these outcomes [406,407]. In terms of cellular mechanistic pathways, myricetin exerted anti-proliferative action on different cancer cells via downregulated expressions of survivin, cyclin D1, Bcl-2, MMP, ERK1/2 and Akt phosphorylation; upregulated expressions p53, Bax, AIF, Bax/Bcl-2 ratio, casapse-3, -9, and PARP-1; increased release of cytochrome C and ROS; and PAK1/ MEK/ ERK mediated signaling [408]. Some combi-

natorial effects of myricetin with gallic acid, naringenin, and radiotherapy are also reported to be efficacious against different cancers [409–411].

5.11. Morin (11)

Morin (3,5,7,29,49-pentahydroxyflavone), is a flavonoid found mostly in the plants of Moraceae family that includes *Maclura pomifera, Maclura tinctoria, Acridocarpus orientalis, Allium cepa, and Psidium guajava* [412–416]. Effectivity of morin against inflammation, oxidative stress, and several other cancers is well documented [417,418]. Earlier, morin was found efficacious in uric acid related disorders [419]. It exhibited serum UA suppressing action where it either inhibited XO or urate anion transporter-1, hence can be used in gout attack [420–422].

Morin reportedly abolished cancer via downregulating the Src, JAK-1, and -2, all of which work through the inhibited STAT3 pathway, eventually mediating anti-proliferative, and anti-metastatic activity [423]. In A-549 cells, morin demonstrated tumor suppressing activity by reducing the colony formation and rate of invasive cell migration, and inhibiting cell viability and proliferation [424]. Here, morin limited the expression miR-135b, a tumor promoter which suppresses CCNG2 gene. In HCT-116 colon cancer cells, it caused caspase-mediated apoptosis via enhancing the expression of Fas receptor, abrogating the Bcl-2 and cIAP-1 expression, increasing the ROS generation, and causing loss to MMP [425]. Morin and MST312 (telomerase inhibitor) combined effectively suppressed STAT3 phosphorylation and telomerase activity, respectively and thereby decreased the colon and breast cancer stem cell population [426]. In SW480 colon cancer cells, it produced anti-proliferative action through causing a rise in ROS generation, cleaved PARP, caspase-3, -8, -9, and Bax, and loss of MMP and Bcl-2 [427]. Morin abolished human colorectal cancer cell HCT-116 growth and proliferation by downregulating TNF-α mediated p65-NF-$_K$B pathway [428]. Combination of morin with esculetin exerted better anti-colon cancer effect through following the β-cateinin/c-myc pathway that in turn altered the process of glycolysis and glutaminolysis [429]. It inhibited tongue squamous cell carcinom CAL27 cell proliferation and migration *in vitro* via upregulating the Hippo signaling and downregulating the nuclear translocation of downstream YAP activity [417]. Morin mediated apoptotic cell death in HL-60 cells via generating ROS, Ca^{2+} ion, reducing $\Delta\Psi_m$ and causing the activation of caspase-3 [430]. It mediated both apoptosis and Sub-G1 phase cell cycle arrest in Nalm-6 and HUT-78 leukemia cells [431]. In human leukemia cells U937, morin was shown to mediate caspase-dependent apoptosis via enhancing the BAD protein expression [432]. In chronic myeloid leukemia cells, morin modulated the miR-188-5p/phosphatase and tensin homolog (PTEN) axis and thereby abrogated the PI3K/Akt pathway to exert its apoptotic effect [433]. It facilitated a significant decrease in MMP and activated caspases-3 and -6, which in turn rationalized its effect in causing apoptosis to leukemic cells [434]. Morin sensitized TOV-21G and SK-OV-3 cells to cisplatin, where it remarkably reduced the galectin-3 expression at the mRNA and protein level [435]. In A2780 and SKOV-3 cells, morin caused reduced expression level of genes related to cell adhesion, and elevated expression level of genes that were suppressed at the time of EMT [436]. The complex of morin and oxovanadium (IV) exhibited apoptotic cell death through loss of MMP and activation of caspase 3/7 in T47D and SKBR3 breast cancer cells [437]. In MDA-MB231 cells, it significantly reduced the levels of MMP-9 secretion, EMT, and Akt phosphorylation to exert its anti-invasive effect [438]. In addition, morin abolished cell adhesion in HUVECs via suppressing vascular cell adhesion molecule 1 (VCAM1), and EMT through mainly decreasing N-cadherin expression [439]. It exhibited potential promise against hepatocellular carcinoma via suppressing the levels of lipid peroxidation, damage to hepatic cells and rescuing the antioxidant systems [440]. Apoptosis was facilitated by morin in hepatocellular cancer, where it upregulated PTEN, Bax/Bcl-2 ratio, caspase-3 and -9, release of cytochrome C and abrogated the Akt-regulated downregulation of GSK-3β that promoted cell cycle arrest at G1/S phase [441]. The anti-proliferative potential of auranofin was facilitated by morin in Hep3B human hepatocellular carcinoma cells where it enhanced the expression of death receptor DR4/DR5, Bax, caspase-3, -8, and -9, suppressed the expression of Bcl-2, and caused ROS generation [442]. In HeLa cells, morin mediated G2/M cell cycle arrest via suppressing the mRNA expression of CDK1, cell division cycle 25C (Cdc25c), survivin, cyclin B1 and checkpoint kinase 2 (Chk2) genes and elevating the mRNA expression of p53, p21 and wee1-like protein kinase (Wee1) genes [443]. In addition, the associated molecular targets that are actively involved in the anti-cervical cancer effect include enhanced mRNA expression level of Bax, BAD, cytochrome C, apoptotic protease activating factor 1 (Apaf-1), caspases-9, -10, DR3, DR5, FasL, fas-associated protein with death domain (FADD), PARP, PI3K, Akt, mTOR, P^{70S6K} and second mitochondria-derived activator of caspase (Smac) genes and reduced expression levels of Bcl-2, Bcl-XL, AMPK, cIAP-1, cIAP-2, PKC and NF-κB. Gold nanoparticle modified morin pH-sensitive liposome demonstrated enhanced anticancer effect in SGC-7901 gastric cancer cells via aggravating the ROS generation [444]. A recent review on the comprehensive anticancer role of morin has accumulated mechanisms like, upregulation of antioxidant activity, induction of cell cycle arrest, downregulation of cell survival proteins, advancement in cell death, interfering with cell invasion and metastasis, and prevention of inflammation are actively involved [445]. Here, the comprehensive molecular targets that are modulated by morin in the cell death pathway include inhibition or downregulation of PI3K, Bcl-2, Bcl-XL, IAP1, IAP2, X chromosome linked IAP and survivin, and upregulation or activation of PTEN, Bax, and cytochrome C, caspases-3 and 9. Moreover, in the cell cycle arresting mechanism, according to the same review, molecular targets like, p21, Wee1, GSK-3β, Wnt5a/b, Wnt3a, and β-catenin are upregulated and cdc25, Cyclin A & B1 complex, AP-1, argyrophilic nucleolar proteins (AGNOR) and PCNA are downregulated.

5.12. Diosmetin (12)

Diosmetin (3, 5, 7-trihydroxy-4′-methoxyflavone), a bioflavonoid generously occurrs in a number of dietary components including oregano spice, oregano leaves, citrus fruits, and plants like, *Citrus sinensis, Rosmarinus officinalis, Galium verum, Rosa agrestis Savi* [446,447]. Pharmacological outcomes of diosmetin include antioxidant, anti-inflammatory, and anticancer effects [448–450]. Diosmetin is also reported as an effective XO inhibitor [54].

Diosmetin works as a cytochrome P450 enzyme CYP1 substrate [451]. Diosmetin being pre-treated with CYP1 inducer 2,3,7,8-tetrachlorodibenzo-p-dioxin, demonstrated anti-proliferative activity in MCF-7 cells [451]. The anti-proliferative activity of diosmetin on MDA-MB-468 human breast cancer and MCF-10A normal breast cells was examined, along with its effects on cell cycle progression [448]. Diosmetin inhibited the proliferation and G1 phase cell cycle progression of MDA-MB-468 cells, as a result of CYP1 enzyme mediated metabolism of diosmetin into luteolin. It demonstrated mentionable anti-proliferative action in MDA-MB-231 cells through enhancing the levels of ROS generation, lactate dehydrogenase release, cell cycle arrest at G0/G1 phase, mitochondrial dysfunction, suppression of Bcl-2 and Cyclin D1 expressions, upregulation of p53, Bax, caspase 3 expression, and cleavage of caspase 9 and 3 [452]. In HepG2 cells, it caused cell cycle arrest

at G2/M phase that was guided through enhanced expression of phospho-ERK, phospho-JNK, p53, and p21 [453]. In the same liver cells, diosmetin mediated apoptosis via increased p53 expression, which followed the TGF-β mediated signaling [454]. Using the same cells again, it was appeared that induction of autophagy by diosmetin was regulated via mTOR pathway [455]. In SKHEP1 and MHcc97H hepatocellular carcinoma cells, diosmetin exhibited anti-invasive property through suppressing the MMP2/9 expression that was mediated by the PKC/MAPK/MMP signaling [456]. Increased expression levels of p53/Bcl-2 and decreased expression levels of NFκB/Notch3 were also being implicated in the anti-proliferative action of diosmetin in liver cancer [457]. Diosmetin was recently reported to exert anti-proliferative and pro-apoptotic activity in HepG2 and HCC-LM3 liver cancer cells as well [458]. It caused G2/M cell cycle arrest in HepG2 cells through targeting the Chk2. Diosmetin exhibited anticancer action on LNCaP and PC3 prostate cancer cells via reducing cyclin D1, CDK2, and CDK4 protein expressions, which generally function in the G0G cell cycle phase [459]. This chemotherapeutic effect was also guided through a reduction in c-myc and Bcl-2 expression and a rise in Bax, $p27^{Kip1}$ and fork head box O3 (FOXO3a) protein expressions. Moreover, diosmetin facilitated apoptosis via suppressing XIAP, and cleaving PARP and caspase-3. It showed ameliorative effects on B16F10 and HUVEC melanoma cells by functioning as an anti-proliferative and anti-migrant agent [460]. In B16F10 cells, it promoted apoptosis through caspase dependent pathway, where it suppressed tube formation and cell migration in HUVEC cells. Here, diosmetin activated caspase-3 via its cleavage and enhanced the cleaved-PARP expression, that in turn caused apoptosis. Diosmetin enhanced the effectivity of paclitaxel in a number of NSCLC cells by mediating apoptosis that was achieved through increased generation of ROS and suppression of the PI3K/Akt/GSK-3β/Nrf2 signaling [461]. In HCT-116 colon cancer cells, it caused cell cycle arrest at G2/M phase, release of cytochrome C, cleavage of caspases, suppressed expression of Bcl-2, NF-ĸB and increased expression of Fas, Bax [449,462]. Diosmetin mediated cytotoxicity and apoptosis in ACHN renal cancer cells via causing enhanced expression of p53 and decreased expression of PI3K/Akt [463]. In K562 leukemia cells, diosmetin mediated apoptosis through activating caspases-3, -7, -8, and TNF-α, where ER-β was observed to be involved [464]. A recent review compared the anticancer properties of diosmetin and tamarixetin, where they came up with a conclusion that diosmetin is a stronger chemotherapeutic agent because of its presence of C3 hydroxyl group at ring C [465].

5.13. Isorhamnetin (13)

Isorhamnetin (3′–methoxy–3,4′,5,7–tetrahydroxyflavone), one of the flavonoids found in various fruits, vegetables and tea, as well as in traditionally used medicinal herbs like *Ginkgo biloba, Persicaria thunbergii* H and *Hippophae rhamnoides* L [466,467]. Along with a number of reported pharmacological potentials, isorhamnetin shows antioxidant, anticancer, and anti-inflammatory activity [468–470]. Various cancer cell types are inhibited by isorhamnetin that include esophageal and gastric cancer, skin, colon, breast, and lung cancer [468,471,472]. The XO inhibitory property of isorhamnetin is already reported that can be employed in the management of gout and oxidative injury mediated via ischemic-reperfusion [367].

Isorhamnetin was found to be effective in three different human colorectal cancer cells, *i.e.*, HT–29, HCT116, and SW480. In all three cancer cells, isorhamnetin exerted anti-proliferative action through suppressing the PI3K–Akt–mTOR pathway, and mediating cell cycle arrest at the G2/M phase [473]. It also exerted chemo-protective action in colon cancer cells that was basically associated with its inflammation suppressing effect, abrogation of oncogenic Src, and nuclear β-catenin, and upregulation of the C-terminal Src kinase (CSK) expression [474]. Isorhamentin mediated anti-proliferative effect in HT-29 and Caco2 cells where caspase 3/7 activity was upregulated [475]. Isorhamentin in Tsoong caused promotion of apoptotic effect in colon cancer cells via repressing the Hsp70 expression [476]. Induction of cell cycle arrest and apoptosis by isorhamnetin in HT-29 cells was mediated via enhanced Bax/Bcl-2 ratio and considerable fall in MMP [477]. In gastric cancer, isorhamnetin amplified the tumor suppressing effect of capecitabine via suppressing the NF-κB signaling pathway [472,478]. The induction of apoptosis by isorhamnetin in the same cancer cells took place via the modulation of peroxisome proliferator-activated receptor γ (PPARγ) pathway. Different variety of breast cancer cells were inhibited by isorhamnetin including ER-positive progesterone receptor-positive MCF-7, T47D, BT474, and ER–PR–HER2 cells BT–549, MDA–MB–231, MDA–MB–468 [468]. In this breast cancer inhibitory role, isorhamnetin enhanced Bax expression, cleaved caspase 3, and reduced Bcl–2 and Bcl–XL expression. The anti-invasive effect of isorhamnetin on MDA-MB-231 cells was due to suppressed level of MMP-2 and -9, that was related to p38 MAPK and STAT downregulation [479]. In MCF-7 cells, it mediated cell cycle arrest and apoptosis through generating increased levels of ROS [480]. In triple negative breast cancer cells, combination of chloroquine and isorhamnetin promoted mitochondrial-mediated apoptosis through ROS-regulated Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)/dynamin-related protein 1 (Drp1) signaling [481]. EGF-dependent neoplastic transformation was inhibited by isorhamnetin in JB6 cells and A431 mouse xenograft model, where the COX-2 was suppressed [471]. The inhibitory pathway of isorhamnetin is followed by blockade of the MEK/ERK/ $p90^{RSK}$ and PI3K/Akt/$p70^{S6K}$ signaling and consequent AP-1 downregulation. In B16F10 melanoma cells, it caused apoptosis via downregulating the PI3K/Akt and NF-κB expression [482]. In PANC-1 cells, isorhamnetin exhibited S-phase cell cycle arrest via suppressing cyclin A [483]. This growth arresting mechanism of isorhamnetin involved reduced phosphorylation of MEK and ERK in the Ras/MAPK signaling pathway. In A-549 cells, isorhamnetin in combination with cisplatin and carboplatin demonstrated better apoptosis induction through causing considerable distortion and depolymerization to microtubules, cell cycle arrest at G2/M phase, decrease in MMP, and upregulation of PARP, and caspases 3, and 9 [484]. Enhanced expression levels of p53, Bax, and caspase-3, and reduced expression levels of Bcl-2, cyclinD1, and PCNA were induced by isorhamnetin to mediated anti-proliferative action in lung cancer cells [485]. Promising anti-lung cancer effect was also observed in A-549 cells where autophagy inhibition and induction of mitochondrial-mediated apoptosis, both were involved [486]. It showed promising metastasis suppressive action in A-549 cells, where EMT was repressed through abrogating the Akt/ERK1/2 signaling [487]. Radiosensitivity to A-549 cells was remarkably increased by isorhamnetin where IL-13 and NF-κB expression were repressed [488]. In oral squamous cell carcinoma cells, isorhamnetin caused paraptotic cell death through mediating cell cycle arrest at G2/M phase, repressing the levels of cyclin B1 and CDC2, generating ROS, and enhancing the phosphorylation levels of ERK cascades [489]. In bladder cancer cells, isorhamnetin facilitated cell cycle arrest and apoptosis through causing increased generation of ROS and repressed AMPK signaling [490]. In androgen-independent DU145 and PC3 prostate cancer cells, isorhamnetin produced anti-proliferative and anti-metastatic action via increased EMT and abrogated expression of MMP-2, -9, and PI3K/Akt/mTOR signaling [491]. In HeLa cells, it caused apoptosis and G2/M phase cell cycle arrest through tubulin depolymerization, repressed expression of cyclin B1, Cdc25C, and Cdc2, and

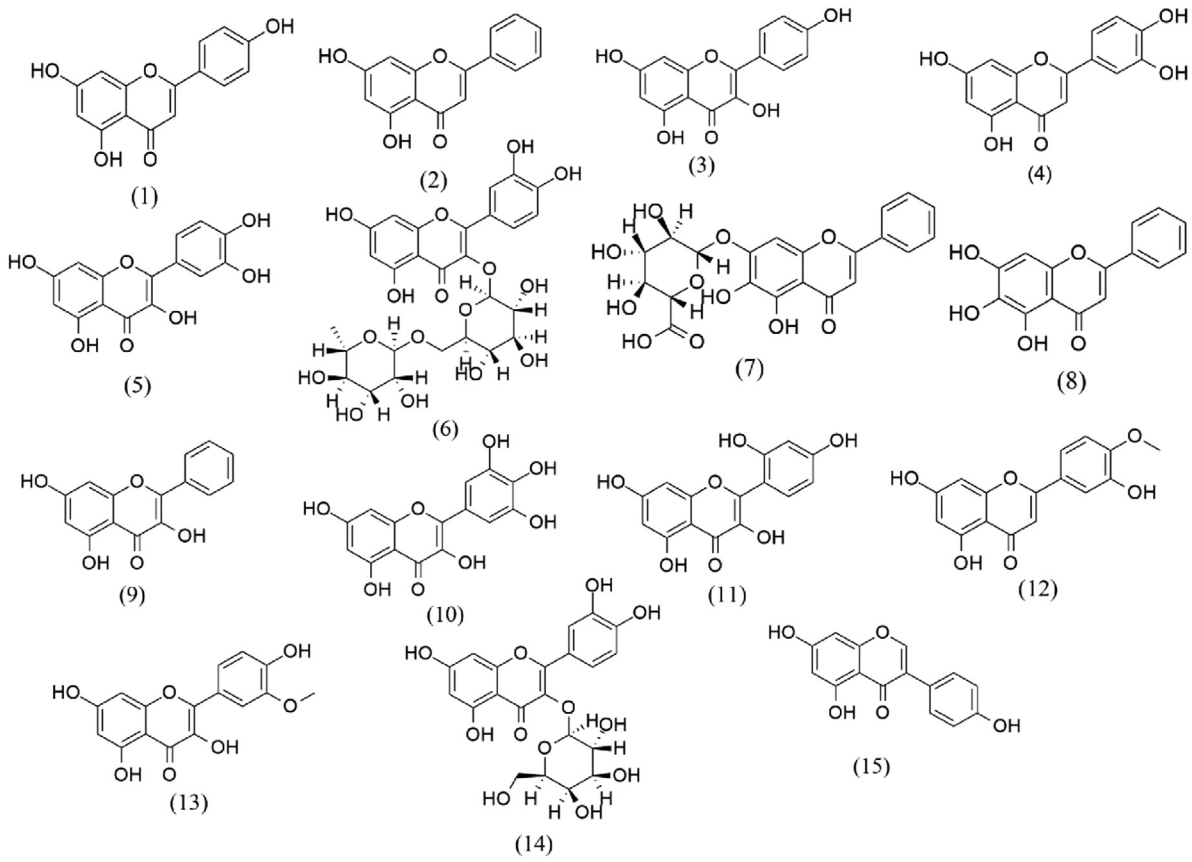

Fig. 2. Structure of discussed flavonoid compounds having cancer chemotherapeutic roles.

increased expression of Chk2, Cdc25C, and Cdc2 phosphorylation [492]. Use of nanomaterial carboxymethyl chitosan as a career of isorhamentin has shown to be effect against nasopharynx cancer [493]. Anticancer effect of different densities of isorhamentin in glioma cells was demonstrated in a report where apoptosis was induced and PI3K/Akt signaling was proposed to be involved in that [494].

5.14. Hyperin (hyperoside) (14)

Hyperin (quercetin-3-O-galactoside), also known as hyperoside is a flavonol glycoside found in herbs like *Hypericum perforatum L, Alpina officinarum, Silybum marianum,* and *Crataegus pinnatifida*, in addition to a number of vegetables and fruits [495]. So far, hyperin is reported for its anti-apoptotic, anti-inflammatory, antidepressant, and anti-hyperglycemic activities [496–498]. Specific studies on the anticancer action of hyperin have revealed that it improves lung, pancreatic, prostate, renal, breast, and skin cancer [499–504]. The XO inhibitory role of hyperin is already reported [54].

The associated events related to the anticancer action of hyperin include inhibition of cell proliferation, induction of apoptosis and cell cycle arrest, and suppression of angiogenesis. Being combined, quercetin and hyperin synergistically demonstrated anticancer effects on 786-O renal cancer cells by significantly reducing the ROS, facilitating caspase3 activation and PARP cleavage, and inhibiting oncogenic miR27a [501]. The same combination mediated apoptosis in human prostate cancer cells through activating caspase3, cleaving PARP, and inhibiting miR21 [504]. Combinatorial effect of quercetin and hyperin is also previous reported in MOLT-4 human leukemia cells [505]. In HL-60 leukemia cells, hyperin remarkably enhanced the anticancer potential of arsenic trioxide through repressing the BAD from phosphorylation, activating caspase-9, enhancing p27 levels, and mediating autophagy by increasing the LC-II expression [506]. In INS-1 and MIA PaCa-2 pancreatic cancer cells, hyperin exhibited apoptotic activity by mediating G2/M phase cell cycle arrest and activation of caspase-3 [507]. Hyperin inhibited human pancreatic cancer cell proliferation and facilitated apoptosis via enhancing the Bax/Bcl-2 and Bcl-XL ratios and suppressing the NF-κB expression and its downstream genes [500]. It followed quite close mechanistic pathway against lung cancer [508]. Effective abrogation of NF-κB and cell proliferation associated signaling; activation of caspase-9 and -3, and induction of cell cycle arrest were also implicated to be involved in the anti-lung cancer effect of hyperin [509]. In A-549 cells, hyperin promoted apoptosis and diminished cell viability through upregulated p38 MAPK and JNK phosphorylation and suppressed level of mitochondrial membrane penetrability [503]. In addition, it facilitated the cytosolic delivery of mitochondrial cytochrome C and apoptosis inducing factor, while at the same time upregulated the caspase3 and 9. The effect of hyperin on NSCLC cells with T790M mutation was shown through anti-proliferative and pro-apoptotic mechanisms where FoxO1 expression was enhanced via colon cancer associated transcript 1 (CCAT1) [510]. The induction of autophagy and apoptosis in NSCLC cells by hyperin was mediated through inhibition of the Akt/mTOR/p70^{S6K} signaling [511]. Hyperin and miR-let7a-5p in combination showed satisfactory synergism against lung cancer mainly through causing G1/S phase cell cycle arrest [512]. In hypoxia-induced A-549 cells, hyperin suppressed cell survival and produced anti-proliferative effect via accumulating ferrous ion and upregulating the AMPK/heme oxygenase-1

(HO-1) signaling [513]. The effect of hyperin on MCF-7 cells and 4T1 cells is well documented [502]. It significantly reduced the Bcl-2 and XIAP levels, enhanced the Bax level and facilitated caspase-3 cleavage. Moreover, ROS were remarkably reduced by hyperin with consequent inhibition of NF-κB activation. In RL952 endometrial cancer cells, hyperin mediated apoptosis through Ca^{2+}-associated mitochondrial dependent pathway [514]. It mediated apoptosis in gastric cancer cells, where tumor growth process was abrogated by reduced expression of Wnt/β-catenin signaling [515]. In U2OS and MG63 osteosarcoma cells, hyperin produced anti-proliferative effect through mediating G_0/G_1 phase cell cycle arrest, and upregulating the levels of osteopontin, runt-related transcription factor 2, TGF-β and bone morphogenetic protein-2 [516]. The anti-skin cancer activity of hyperin was also evident where apoptosis and autophagy were induced via downregulated expressions of the PI3K/Akt/mTOR/p38 MAPK signaling, and upregulated expression of the AMPK signaling [499]. Hyperin effectively sensitized the ovarian cancer cells to cisplatin through progesterone receptor membrane component (PGRMC)1 mediated autophagy that was later used by hyperin to eventually cause apoptosis [517]. Caspase mediated apoptosis and upregulation of the p53 signaling was observed to be one of the mechanistic pathways in the anti-colon cancer activity induced by hyperin in SW620 cells [518]. In HT-29 cells, hyperin and rutin combined mediated apoptosis through upregulation of the mitochondria-induced cell death mechanism that took place through regulation of Bcl-2-associated X protein and Bcl-2 expression, eventually causing cleaved caspases-3, -8, -9 and PARP activation [519]. In HeLa and C-33A cells, hyperin showed anti-proliferative action via suppressing the expression of c-myc and regulating the transferrin receptor protein *TFRC* genes [520].

5.15. Genistein (15)

Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) is an isoflavone found in plant-based products like soybean, lupin, fava beans, kudzu, psoralea, coffee, in herbal plants including *Flemingia vestita, F. macrophylla* and in *Maackia amurensis* cell cultures [521–524]. Some of the reported pharmacological benefits of genistein include antioxidant, anti-inflammatory, antibacterial, antiviral, and antiangiogenic properties [525–529]. Epidemiological studies have shown that the intake of dietary-rich isoflavones reduced the risk of various human cancers. Genistein works against a number of cancers such as esophagus, colon, prostate, liver, lung, ovarian, bladder, brain, gastric, neuroblastoma, and breast [530–534]. It is also reported to tackle oxidative insult by ischemic-reperfusion via inhibiting XO and COX-2, ascertaining its role as an anti-gout agent [367,368].

Genistein has the capacity to act as an anti-proliferative agent in colon cancer HT-29 cells by mediating G2/M phase cell cycle arrest and consequent apoptosis [534]. Here, genistein enhanced the Bax and $p21^{WAF1}$ expression and reduced the Bcl-2 level to induce apoptosis. Interestingly, quite close mechanistic pathway of cell growth inhibition by genistein was observed in prostate adenocarcinoma and NSCLC cells [531,535]. In another 3 NSCLC cells, genistein facilitated the tumor suppressing activities of EGFR-tyrosine kinase inhibitors due to remarkable decrease in the DNA-binding of NF-κB [536]. The ability of genistein to inhibit cell viability and induce apoptosis in A-549 cells followed the downregulation of the PI3K/Akt/HIF1α/ and NFκB/COX2 signaling [537]. The lung cancer inhibitory mechanisms of genistein in several other cancer cells include a p53 independent pathway, downregulation of FoxM1 protein, and miR-27a-mediated MET signaling pathway [538–542]. The anticancer mechanism of this compound in SK-OV-3 ovarian and HGC-27 gastric cancer cells is also associated with G2/M phase cell cycle arrest [543,544]. In MDA-MB-231 cells, genistein performed inhibitory cell growth activity by suppressing EGF and Akt mediated NF-κB signaling [532]. Human colorectal cancer cells metastasis was abolished by genistein via Fms related tyrosine kinase 4 (FLT4) suppression, a metastatic disease marker [545]. A number of cell lines, including KNS60, U251MG, A172, and ONS76 were studied to detect anti-tumor activities in brain where genistein caused cell cycle arrest by upregulating p21 and cyclin B1 and CDK1 [546]. In HepG2, Bel-7402, and SMMC7721 cells, genistein abolished tumor metastatic marker EMT, which is TGF-β mediated [547]. The combinatorial effects of genistein with FOLFOX (oxaliplatin) and topotecan were reported against human colorectal and prostate cancers [548,549]. In addition, combination of genistein with trichostatin A and all-trans retinoic acid demonstrated effective outcomes against human lung cancers [550,551].

6. Clinical or preclinical applications of flavonoids for cancer treatment

Despite numerous reports in favor of flavonoids for their *in vitro* chemotherapeutic properties, a fewer number of evidences are found where flavonoids have been reported as promising anticancer agents in *in vivo*, pre-clinical or clinical studies. This is due to their poor *in vivo* bioavailability [552]. To overcome this drawback, advanced delivery strategies, *e.g.*, liposome, nanoparticles, specific carriers, etc. have been developed [553–555]. However, a higher dosage of flavonoids was reported as safe for *in vivo* applications, although uncontrolled intake of flavonoids might cause gastro-intestinal symptoms, haemolytic anaemia, hepatotoxicity, and contact dermatitis [556,557]. Genistein demonstrated promising potentials in breast and colorectal cancer prevention in *in vivo* studies [558,559]. It was found as a potent anticancer agent in experimental cancer research as well [560]. In addition, genistein combined with FOLFOX or FOLFOX-Bevacizumav was found safe when used against metastatic colorectal cancer in a phase I/II pilot study [549]. In cancer chemotherapy, quercetin was used in combination with docetaxel to improve the anti-metastatic property of the drug by abrogating the AKT/MMP-9 signaling [561]. This synergistic effect was evidenced by both *in vitro* and *in vivo* studies [562]. Nano capsulated delivery of quercetin in *in vivo* rat models evidenced potent prevention from hepatocarcinogenesis [563]. Morin and its several derivatives have been found promising in a number of *in vivo* studies where cancers, like breast, liver, ovarian and hepato-renal carcinoma were ameliorated [564]. Apigenin loaded nanoparticle delivery in rats showed substantial decrease in hepatocellular carcinoma [565]. In a proof concept clinical study, a well-known herbal agent MB-6 that was rich in various flavonoids demonstrated notably decreased progression of colorectal cancer in patients when compared to the placebo group [566]. Polyphenon E, which is a decaffeinated green tea catechin mixture, was clinically established as an effective treatment option against lung, colon, and bladder cancers [567]. The potential clinical application of kaempferol against breast cancer was proposed to be improved by employing targeted drug delivery systems such as, nanostructured lipid carriers, mesoporous targeted delivery, etc. [568].

7. Small molecules from anti-gout dietary sources: a new hub for anticancer lead

Through this review, we attempted to build a logical correlation among mechanisms of XO inhibiting compounds for the management of cancers and inflammatory disorders like gout and arthritis. Here, we also reported 40 natural plant sources along with their dietary formulations that are traditionally used to treat gout and arthritis by local medical practitioners (Table 1) with a view to following up a number of anti-gout/arthritis natural remedies that

Table 1
Potential plants that are traditionally used to treat gout and are hypothesized to be effective in cancer treatments

SN	Scientific name	Family	Local name	Parts used	Dietetic supplementation or formulation	Isolated flavonoids	References
1	*Abutilon indic um* L.	Malvaceae	Horin kani	Whole plant	Pill made from crushed or paste of whole plants is taken thrice daily for 7 d.	Luteolin, Chrysoeriol, Luteolin 7-O-beta-glucopyranoside, Chrysoeriol 7-O-beta-glucopyranoside, Apigenin 7-O-beta-glucopyranoside, Quercetin 3-O-beta-glucopyranoside, Quercetin 3-O-alpha-rhamnopyranosyl (1 –> 6)-beta-glucopyranoside	[577,578]
2	*Aloe vera*	Liliaceae	Gritakumari	Internal part of stems	Internal portion of the leaves or stem is separated which is whitish in color and as like as jelly (turbid, semisolid). To be taken as a juice, daily one time.	Apigenin, luteolin, isovitexin, isoorientin, saponarin, lutonarin, kaempferol, quercetin, myricetin, quercitrin, rutin, catechin,epicatechin	[579,580]
3	*Anisomeles indica L. Kuntze*	Lamiaceae	Jharbo-horin Sing	Leaves	Leaf juice is given orally; one teaspoonful, twice daily for 4–5 d.	Pedalitin, apigenin, scutellarein 7-O–d-glucuronide methyl ester, apigenin 7-O-glucuronide, (terniflorin	[581–583]
4	*Azadirachta indica A.Juss.*	Meliaceae	Neem	Leaves	Liquid extract of leaves to be used.	8-prenylnaringenin, 4′-O-methyl-8-prenylnaringenin, 3′-prenylnaringenin, euchrestaflavanone, kaempferide, 3-O-methylmearnsetin, 3-methoxy-3′-prenylkaempferol	[579,584]
5	*Boerhaavia repens* L.	Nyctaginaceae	Punornova	Roots, stems, leaves	Leaves and *juvenile* stems, roots are mashed and tablets are made from the mashed product. Then dry it. To be used three times daily	eupalitin 3-O-â-Dgalactopyranosyl-(1f2)-â-D-glucopyranoside, eupalitin 3-O-â-D-galactopyranoside, 6-methoxykaempferol 3-O-â-D-(1f6)-robinoside	[579,585]
6	*Cannabis sativa* L.	Cannabaceae	Bhang	Leaf, roots	One teaspoon powder obtained from crushed and dried leaf is added to water and taken once orally.	cannflavin A, cannflavin B	[586,587]
7	*Cassia fistula* L.	Caesalpiniaceae	Bandarlathi	Leaves, pulps,	Fruits pulp is considered good application for gout, taken daily for few days	fistulaflavonoid B, fistulaflavonoid C, licoisoflavone, (3S)-30,7-dihydroxy-20,40,50,8-tetramethoxyisoflavan, (3S)-7-hydroxy-20,30,40,50,8-penta-methoxyisoflavan, morusyunnansins F, (2S)-20,40-dihydroxy-7-methoxy-8-prenyl-flavan	[588,589]
8	*Ficus religiosa* L.	Moraceae	Ashwattha	Root	Chewed	Bengalenosides, 5, 7 Dimethyl ether of Leucoperalgonidin-3-0-α-Lrhamnoside and 5, 3 dimethyl ether of leucocyanidin 3-O-β Dgalactosyl cellobioside, and 5, 7, 3 trimethoxy leucodelphinidin 3-O-α-L-Rhamnoside	[590,591]

(*continued on next page*)

Table 1 (*continued*)

SN	Scientific name	Family	Local name	Parts used	Dietetic supplementation or formulation	Isolated flavonoids	References
9	*Gnaphalium pulvinatum* Delile.	Asteraceae	Banpalang	Leaves	Taken leaves paste	n/a	[592]
10	*Hemidesmus indicus L. R.Br.*	Apocynaceae	Onontomul	Root	½ spoon taken in the morning once	wererutin, hyperoside, quercetin, iso-quercitrin	[593,594]
11	*Jatropha curcas* L.	Euphorbiaceae	Shet verenda,	Young leaves	Powder - four tea spoons + one cup water taken orally two times	rutin, myricetin, daidzein, apigenin	[594–596]
12	*Justicia gendarussa* Burm.	Acanthaceae	Basak pata	Leaves, roots	Juice from leaves is mixed with seeds of Nigella sativa L. (Ranunculaceae) and rhizomes of Zingiber officinale Roscoe (Zingiberaceae) and taken Leaf juice is taken thrice daily (one cup amount)	6,8-di-C-α Larabinocylapigenin or gendarusin A	[597–600]
13	*Lannea coromandelica Houtt. Merr.*	Anacardiaceae	Jiala	Barks, stems	Decoction of bark is given in 1/2–1 ounces dose in gout. 10 g of bark is boiled in four to five cups of water until the liquid is reduced to one cup, cooled, and strained before use.	3′,5-dihydroxy-4′,7 dimethoxydihydroflavonol, 4′,5,7-trimethoxydihydroflavonol, 4′,7-di-O-methy dihydroquercetin, 4′,7-di-O-methyldihydrokaempferol, 4′-O-methyldihydroquercetin,	[577,601,602]
14	*Momordica charantia* L.	Cucurbitaceae	Korla	Root, seed, fruit	Juice taken one time in morning (0 to 100 mL of fruit juice) on an empty stomach or taken as vegetable (the bitter taste is considered by the Kavirajes as one of the most healing tastes; a bitter substance can heal a lot of imbalances in the mind and body) Leaf juice rubbed. One teaspoon leaf juice + few drops of honey, thrice daily	Catechin and epicatechin	[594,603,604]
15	*Moringa oleifera* Lam.	Moringaceae	shajina	Leaves, fruits, barks, flowers	Pills are made from a paste of leaves and fruits and taken thrice daily for 8 d. Leaves and fruits are edible; they are cooked and eaten as vegetable. Four to six spoons of bark juice are taken orally daily.	Myricetin, Quercetin and Kaempferol	[605–608]
16	*Ocimum gratissimum* L.	Lamiaceae	Midareissa	Leaves	Leaf juice along with honey or sugar is prescribed orally; two teaspoons, thrice daily for 3–5 d.	apigenin 6,8-di-C-glucoside, quercetin 3-O xylosyl(1‴→2″) galactoside, luteolin 5-O-glucoside, luteolin 7-O-glucuronide, quercetin 3-O-(6″-O-malonyl)glucoside	[585,605,609]
17	*Scoparia dulcis* L.	Scrophulariaceae	Chinipata, Chinigura	Leaves	One tablespoon of leaf juice is taken orally twice daily.	apigenin, scutellarein, luteolm, vlcenm-2, lmarm, vitexm, lsovltexin, scutellarm, scutellarm methyl ester, luteolm 7-glucoside	[610,611]
18	*Spilanthes calva* DC.	Asteraceae	Marhatitiga, Nakful	Leaves	Half a cup of leaf juice is taken orally once or twice a day.	6-(3-methylbut-1-enyl)-5,7-dimethoxy-4′-hydroxy flavone	[610,612]

(*continued on next page*)

Table 1 (*continued*)

SN	Scientific name	Family	Local name	Parts used	Dietetic supplementation or formulation	Isolated flavonoids	References
19	*Stephania glabra Roxb. Miers*	Menispermaceae	Pir guruch	Leaves, stems	Powder from dried leaves and stems is mixed with cold water and honey. One teaspoonful of the mixture is taken twice daily for 2 wk.	40,5,7 -trihydroxy-8-C-glucosylisoflavone	[613,614]
20	*Syzygium cumini L. Skeels*	Myrtaceae	Jam	Bark, internal part of seed	Powder is made from dry fruits, and then the powder is eaten with water three times daily.	isoquercitrin, quercetin, kaempferol,	[579,615]
21	*Terminalia chebula* Retz.	Combretaceae	Hortoki	Fruit	Fruit powder is taken orally with jaggery.	Rutin, Quercetin, Luteolin, Isoquercetin, 3-Methoxy quercetin, 3,4′-Dimethoxy quercetin	[606,616]
22	*Vitex negundo*	Verbenaceae	Nishinda	Leaves Roots	Leaves are mashed and tablets are made from the mashed product. Then dry it. To be used 4 times daily. Roots are collected on Friday/ Full moon and washed and shade dried. It is grounded with honey and put in an earthen vessel (Handia). This vessel is kept under the heap of paddy seeds for 31 d. Pills (8–10 gms) are made after proper mixing, and one pill per day is given for the treatment of rheumatism, gout, and other joint pain for 41 d. The treatment can be continued for up to 1 y for complete cure of the diseases.	5-Hydroxy-7, 4′-dimethoxy flavone, 5,7-Dihydroxy-6,4′-dimethoxy, Luteolin, Luteolin-7-O-β-D-glucoside, 7, 8-Dimethyl herbacetin-3-rhamnoside, Vitegnoside, so-orientin, Corymbosin, Vitexicarpin	[579,617]
23	*Alpinia nigra (Gaertn.) B.L. Burtt.*	Zingiberaceae	Tera gach, Jongli deodar	Stem, rhizome	Three cups of juice obtained from macerated stems are taken three times daily after meal. 1 kg rhizome is boiled in 4 L water until the final volume is 2 L. One tablespoonful of the decoction is taken orally three times daily after meals.	galangin, pinocembrin, kaempferide-4′-methylether, kaempferol, kaempferol-3-O-β-d-glucopyranoside	[618,619]
24	*Aglaonema hookerianum Schott*	Araceae	Logati	Root	One tablespoonful decoction prepared from roots is taken orally twice daily until cure.	n/a	[619]
25	*Knema bengalensis W.J. de Wilde*	Myristicaceae	Ramdala	Bark	One tablespoonful of decoction prepared from bark is taken orally every morning on an empty stomach until cured.	n/a	[619]
26	*Mesua ferrea L.*	Clusiaceae	Nageshwar	Flower	Flowers are taken with water	Mesuaferrin-A	[620,621]
27	*Paederia foetida L.*	Rubiaceae	Gondo madok	Leaf	Juice obtained from macerated leaves is taken with sugar	n/a	[622]

(*continued on next page*)

Table 1 (*continued*)

SN	Scientific name	Family	Local name	Parts used	Dietetic supplementation or formulation	Isolated flavonoids	References
28	*Paederia scandens L.*	Rubiaceae	Gandhali	Leaves	Leaves are cooked with rice and taken one or 2 d in the treatment of rheumatism and gout.	Kaempferol, Quercetin, Kaempferol 3-O-glucoside, Kaempferol 3-O-rutinoside, Kaempferol 3-O-rutinoside-7-O-glucoside, Kaempferol 7-O-glucoside, Quercetin 3-O-glucoside, Quercetin 3-O-rutinoside, Quercetin 3-O-rutinoside-7-O-glucoside, Quercetin 7-O-glucoside, Delphinidin, Pelargonidin, Peonidin, Malvidin, Quercetin 3-O-rutinoside-7-O-xylosylglucoside, Linarin, Diadzein	[623,624]
29	*Andrographis paniculata (Burm.f.) Wall. ex Nees*	Acanthaceae	Kalamegh, Kalibahu	Roots	Pasted with soaked rice and made half-baked chapattis and taken internally for 1 wk for quick recovery	7-O-methylwogonin, apigenin, onysilin and 3,4-dicaffeoylquinic acid	[623,625]
30	*Calotropis procera (Aiton.f.) Dryand.*	Asclepiadaceae	Sweto, Arkho	Leaves	Leaves are ground with the leaves of *Ricinus cummunis*, *Datura metel*, and alum (after exude out water by heating on hot iron) in equal quantity and made pills. Each pill (3 gms) is given in the morning and evening with hot water for 15–20 d in the treatment of rheumatism.	kaempferol-3-O-rutinoside, isorhamnetin-3-O-rutinoside, quercetin-3-O-rutinoside, 5-hydroxy-3,7-dimethoxyflavone-4′-O-β-glucopyranoside	[623,626]
31	*Polyalthia longifolia (Sonner) Thwaites*	Annonaceae	Devdaru	Stem bark	Stem bark is dried, powdered, and given orally in the treatment of gout for 7 d	Quercetin, quercetin-3-O—glucopyranoside, kaempferol-3-O–rhamnopyranosyl-(1-6)—galactopyranoside, kaempferol-3-O–rhamnopyranosyl-(1-6)—glucopyranoside, rutin, allantoin	[623,627]
32	*Nyctanthes arbor*	Verbenaceae	Shefali	Leaf	Tablets are prepared from the dried and mashed leaf. Two tablets should be taken thrice daily.	n/a	[628]
33	*Ageratum conyzoides*	Asteraceae	Oshoni shak	Leaf, stem	Juices from crushed leaves and stems are orally administered	5′-methoxynobiletin, linderoflavone B, 5,6,7,3′,4′,5′-hexamethoxyflavone, 5,6,8,3′,4′,5′-hexamethoxyflavone, eupalestin, quercetin, quercetin-3-rhamnopiranoside, kaempferol, kaempferol -3-rhamnopiranoside, kaempferol 3,7-diglucoyside	[598,628]
34	*Santalum album*	Santalaceae	Sada-chandan	Stems	Stems are mashed and tablets are made from the mashed product. To be taken three times daily	vicenin-2, vitexin, isovitexin, orientin, isoorientin. chrysin-8-C-beta-D-glucopyranoside, chrysin-6-C-beta-D-glucopyranoside, and isorhamnetin.	[628,629]

(*continued on next page*)

Table 1 (*continued*)

SN	Scientific name	Family	Local name	Parts used	Dietetic supplementation or formulation	Isolated flavonoids	References
35	*Pterocarpus santalinus*	Fabaceae	Raktachandan	Stems, leaves	Leaves and stems are mashed and tablets are made from the mashed product. To be taken four times daily.	Taxifolin, dihydrokaempferol, naringenin	[628,630]
36	*Mimosa pudica*	Fabaceae	Laal lojjaboti	Leaf	Tablets are made from dried and mashed leaves. To be taken three times daily.	n/a	[628]
37	*Xanthium indicum J. Koenig ex Roxb.*	Asteraceae	Hagra gach	Leaves, stems	Leaves are boiled with stems in water for 10 min. Then they are taken in the cooked form like chocchori. Alternately, stems are slightly boiled in a little water, and juice obtained from those crushed stems is taken. For severe rheumatic pain, the juice has to be taken twice daily in the morning and evening for straight 7 d, or if the pain is severe then for straight 21 d.	n/a	[631]
38	*Ocimum americanum L.*	Lamiaceae	Bon tulshi	Bark Leaf	Bark of *Terminalia belerica* (Gaertn.) Roxb. is mixed with bark of *Terminalia chebula*, leaf juice of *Ocimum americanum,* and bark of *Terminalia arjuna* (Roxb.) Wight & Arn.to prepare tablets. One tablet is orally taken thrice daily after meal until cure.	Scutellarein, luteolin, cirsiliol, apigenin, pilosin, cirsimaritin, cirsilineol, ladanein, 5-desmethylsinensitin, xanthomicrol, 8-hydroxysalvigenin, nevadensin, acacetin, pectolinarigenin, genkwanin, 5-desmethylnobiletin, salvigenin, gardenin B and apigenin 7,4′-dimethyl ether	[599,632]
39	*Terminalia arjuna Bedd.*	Combretaceae	Arjun	Bark	Pill made from bark powder is taken twice daily for 21 d	Luteolin, Baicalein, Arjunone, Kempferol, Quercetin, Apigenin	[608,633]
40	*Piper chaba W. Hunter*	Piperaceae	Machmachunda	Leaf	Leaves are fried in oil and taken twice daily for 7 d.	n/a	[608]

might be good candidates for selective screening of anti-cancer leads.

Ethno medicine still strongly prevailed on customs of population in spite of dominancy of allopathic medicine. People, especially from rural and tribal regions are highly dependable on the crude medicines derived from plants made by so-called Kobiraj, local healers, Baiddyas and herbal practitioners as modern treatment facilities in that regions are negligible. In such regions, the mortality and morbidity rate by malicious diseases is very high due to costly treatment system and proper diagnosis [569]. As a result, significant part of this population seeks cure in ethno medicine for a wide range of ailments like infection, fever, pain, inflammation, gout, arthritis, rheumatoid arthritis, common cold, diarrhea, and even fatal disease cancer as they are comparatively cheap and available. Some people interestingly get satisfactory treatment and recover but such cases are not unveiled due to huge communication gap between traditional and modern treatment. Besides the local practitioners always fight shy of expressing and sharing their treatment procedures. It would be very rational and fruitful approach if we could gather more information from those practitioners and utilise it for drug screening. But finding potential anticancer drugs based on traditional treatment is very much difficult. That's why, in this study we used the general mechanisms of gout and arthritis treatment that are very closely related to a specific part of some anticancer drugs' mechanisms to find latent and promising edible medicinal plants (Table 1) as well as flavonoids that might be used for screening of newer anticancer agents. Some of these sources have already been screened for anticancer drugs and cytotoxicity profiles that have provided prospective results. A number of novel anticancer constituents have also been isolated from those plants such as 6-shogaol from *Zingiber officinale* Roscoe [570], papain, lycopene, isothiocyanate from *Caria papaya* L. [571], α-amyrin, β-amyrin from *M. ferrea* L. [572], kuguacin J from *Momordica charantia* Linn. [573], polygodial, quercetin from *Persicaria hydropiper* (L.) Delarbre [574], niazimicin from *Moringa oleifera* Lam [575], eugenol, luteolin, β sitosterol from *Ocimum sanctum* Linn. [576]. Some natural flavonoids for example chrysin, apigenin, luteolin, kaempferol, quercetin, etc. are either used in the treatment of gout, arthritis, and cancer where their IC_{50} values towards xanthin oxidase are very comparable with the IC_{50} value of standard anti-gout drug Allopurinol. Besides some anticancer and antigout natural compounds share same receptors for their actions like colchicine and their analogues. So this hypothesis proved that, unknown compounds that are substrates for xanthin oxidase like mercaptopurine, either can't produce uric acid but competitively inhibit XO or unknown compounds analogous to Allopurinol or

colchicine may be present in anti-gout natural sources resulting relief from gout may have very promising anticancer potential. Such approach might undoubtedly be very novel as well as effective to find out interesting leads for cancer research.

8. Conclusion

This review has shown the rationale of the hypothesis that anti-gout compounds from natural sources can be the depot of anticancer constituents. The relative cross talk between anti-gout and anticancer substances has evolved considerably of late. Yet, more precise research are still to be conducted on the closely associated mechanistic pathways of anti-gout and anticancer compounds. As the incidences of a number of cancers are on the rise worldwide, preventive and multiple treatment strategies are highly regarded these days. This review demands for detailed laboratory-based research on the selective mechanisms of anti-gout substances on chemotherapy and chemoprevention. One of the main responsibilities of the public health departments is to conduct trail-based studies on prospective disease preventing substances, so that prevalence of that particular disease can be managed into a particular area. These kinds of field level clinical trials might be conducted on the mentioned compounds in order to assess the chemotherapeutic and chemopreventive actions. Also, as most of the discussed compounds are from dietary sources, long term plan might be undertaken by the nutritionists and food research institutes to employ these compound containing foods in daily diets as to suppress the incidences of various cancers. Fig. 2

Acknowledgments

MSR and MAS proposed the review concept. MSR, MAS, MAI, and OI wrote the manuscript and depicted the schematic diagram and chemical structures. PCS collected information, performed extensive literature review and prepared the table of the plants list demonstrating antigout properties. AI and JSG supervised and critically reviewed this project.

Funding for open access charge

Universidade de Vigo/CISUG.

Declaration of competing interests

The authors declared no conflict of interest.

References

[1] Finkel R, Clark MA, Cubeddu LX, Harrey R A, Champe P C. Lippincott's Illustrated Review Pharmacology. 4th. Pliladelphia: Lippincott Williams & Wilkins; 2009.
[2] Chen LX, Schumacher HR. Gout: an evidence-based review. J Clin Rheumatol 2008;14(5 Suppl):S55–62.
[3] Schlesinger N. Diagnosing and treating gout: a review to aid primary care physicians. Postgrad Med 2010;122(2):157–61.
[4] Gilman AG, Goodman L S, Rall T W, Murad F. Goodman and Gilman's the pharmacological basis of therapeutics. 7th ed. New York: Macmillan; 1985.
[5] Sneader W. Drug discovery: a history. West Sussex: John Wiley & Sons; 2005.
[6] Robins RK. Potential purine antagonists. I. Synthesis of some 4, 6-substituted pyrazolo [3, 4-d] pyrimidines1. J Am Chem Soc 1956;78(4):784–90.
[7] Wang W, Xu D, Wang B, Yan S, Wang X, Yin Y, et al. Increased risk of cancer in relation to gout: a review of three prospective cohort studies with 50,358 subjects. Mediators inflamm 2015;2015:1–6 Article ID 680853.
[8] Lee JS, Myung J, Lee HA, Hong S, Lee CK, Yoo B, et al. Risk of cancer in middle-aged patients with gout: a nationwide population-based study in Korea. J Rheumatol 2021;48(9):1465–71.
[9] Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V, et al. Regulation of uric acid metabolism and excretion. Int J Cardiol 2016;213:8–14.
[10] Pedley AM, Benkovic SJ. A new view into the regulation of purine metabolism: the purinosome. Trends Biochem Sci 2017;42(2):141–54.
[11] Yin J, Ren W, Huang X, Deng J, Li T, Yin Y, et al. Potential mechanisms connecting purine metabolism and cancer therapy. Front Immunol 2018;9:1697.
[12] Fridley BL, Batzler A, Li L, Li F, Matimba A, Jenkins G, et al. Gene set analysis of purine and pyrimidine antimetabolites cancer therapies. Pharmacogenet Genomics 2011;21(11):701.
[13] Parker WB. Enzymology of purine and pyrimidine antimetabolites used in the treatment of cancer. Chem Rev 2009;109(7):2880–93.
[14] Fini MA, Elias A, Johnson RJ, Wright RM, et al. Contribution of uric acid to cancer risk, recurrence, and mortality. Clin Transl Med 2012;1(1):1–15.
[15] Levine W, Dyer AR, Shekelle R B, Schoenberger J A, Stamler J, et al. Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. J Clin Epidemiol 1989;42(3):257–67.
[16] Petersson B, Trell E. Raised serum urate concentration as risk factor for premature mortality in middle aged men: relation to death from cancer. Br Med J (Clin Res Ed) 1983;287(6384):7–9.
[17] Petersson B, Trell E, Henningsen N C, Hood B, et al. Risk factors for premature death in middle aged men. Br Med J (Clin Res Ed), 1984;288(6426):1264–8.
[18] Yiu A, Van Hemelrijck M, Garmo H, Holmberg L, Malmström H, Lambe M, et al. Circulating uric acid levels and subsequent development of cancer in 493,281 individuals: findings from the AMORIS Study. Oncotarget 2017;8(26):42332.
[19] Johnson RJ, Nakagawa T, Sanchez-Lozada L G, Shafiu M, Sundaram S, Le M, et al. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes 2013;62(10):3307–15.
[20] Xie Y, Xu P, Liu K, Lin S, Wang M, Tian T, et al. Hyperuricemia and gout are associated with cancer incidence and mortality: a meta-analysis based on cohort studies. J Cell Physiol 2019;234(8):14364–76.
[21] Ahmadnezhad M, Arefhosseini S R, Parizadeh M R, Tavallaie S, Tayefi M, Darroudi S, et al. Association between serum uric acid, high sensitive C-reactive protein and pro-oxidant-antioxidant balance in patients with metabolic syndrome. BioFactors 2018;44(3):263–71.
[22] Erlinger TP, Platz E A, Rifai N, Helzlsouer K J, et al. C-reactive protein and the risk of incident colorectal cancer. Jama 2004;291(5):585–90.
[23] Saito K, Kihara K. C-reactive protein as a biomarker for urological cancers. Nat Rev Urol 2011;8(12):659.
[24] Zhang SM, Lin J, Cook N R, Lee I M, Manson J E, Buring J E, et al. C-reactive protein and risk of breast cancer. J Nat Cancer Inst 2007;99(11):890–4.
[25] Bharti R, Dey G, Mandal M. Cancer development, chemoresistance, epithelial to mesenchymal transition and stem cells: a snapshot of IL-6 mediated involvement. Cancer Lett 2016;375(1):51–61.
[26] Sethi G, Sung B, Aggarwal BB. TNF: a master switch for inflammation to cancer. Front Biosci 2008;13(2):5094–107.
[27] Alemu ID, Daba TM. Gloriosa, a source of colchicine: review article. Int J Biol Chem Sci 2016;10(4):1888–93.
[28] Bharathi P, Philomina D, Chakkaravarthi S. Antimitotic effect of colchicine from six different species of gloriosa in onion roots (Allium cepa). J. Med. Sci 2006;6(3):420–5.
[29] Gumustas M, Polat D Ç, Kılıç C S, Akalın K, Ozkan S A, Coşkun M, et al. Comparison of seeds of colchicum speciosum and gloriosa superba in respect to colchicine and colchicoside contents by RP-LC. Nat Prod Commun 2016;11(3):397–400.
[30] Mukhopadhyay MJ, Mukhopadhyay S. A biotechnological approach for enhancement of colchicine accumulation in Iphigenia indica Kunth. J Plant Biochem Biotechnol 2008;17(2):185–8.
[31] Mukhopadhyay MJ, Mukhopadhyay S, Sen S. In vitro propagation of Iphigenia indica, an alternative source of colchicine. Plant Cell Tissue Organ Cult 2002;69(1):101–4.
[32] Tripathi K. Essentials of medical pharmacology. New Delhi: JP Medical Ltd; 2013.
[33] Shi Q, Chen K, Morris-Natschke S L, Lee K H, et al. Recent progress in the development of tubulin inhibitors as antimitotic antitumor agents. Curr Pharm Des 1998;4(3):219–48.
[34] Van Hoorn DE, Nijveldt R J, Van Leeuwen P A, Hofman Z, M'Rabet L, De Bont D B, et al. Accurate prediction of xanthine oxidase inhibition based on the structure of flavonoids. Eur J pharmacol 2002;451(2):111–18.
[35] Owen PL, Johns T. Xanthine oxidase inhibitory activity of northeastern North American plant remedies used for gout. J Ethnopharmacol 1999;64(2):149–60.
[36] Xu H, Li C, Mozziconacci O, Zhu R, Xu Y, Tang Y, et al. Xanthine oxidase–mediated oxidative stress promotes cancer cell-specific apoptosis. Free Radic Biol Med 2019;139:70–9.
[37] Yang H-C, Nguyen P A A, Islam M, Huang C W, Poly T N, Iqbal U, et al. Gout drugs use and risk of cancer: a case-control study. Joint Bone Spine 2018;85(6):747–53.
[38] Wills CA, Liu X, Chen L, Zhao Y, Dower C M, Sundstrom J, et al. Chemotherapy-induced upregulation of small extracellular vesicle-associated PTX3 accelerates breast cancer metastasis. Cancer Res 2021;81(2):452–63.
[39] Ling X, Bochu W. A review of phytotherapy of gout: perspective of new pharmacological treatments. Pharmazie 2014;69(4):243–56.
[40] Arafat OM, Tham S Y, Sadikun A, Zhari I, Haughton P J, Asmawi M Z, et al. Studies on diuretic and hypouricemic effects of Orthosiphon stamineus methanol extracts in rats. J Ethnopharmacol 2008;118(3):354–60.

[41] Nessa F, Ismail Z, Mohamed N. Xanthine oxidase inhibitory activities of extracts and flavonoids of the leaves of Blumea balsamifera. Pharm Biol 2010;48(12):1405–12.
[42] Yumita A, Suganda AG, Sukandar EY. Xanthine oxidase inhibitory activity of some Indonesian medicinal plants and active fraction of selected plants. Int J Pharmacy Pharm Sci 2013;5:293–6.
[43] Budisan L, Gulei D, Jurj A, Braicu C, Zanoaga O, Cojocneanu R, et al. Inhibitory effect of CAPE and kaempferol in colon cancer cell lines—possible implications in new therapeutic strategies. Int J Mol Sci 2019;20(5):1199.
[44] Khoo BY, Chua SL, Balaram P. Apoptotic effects of chrysin in human cancer cell lines. Int J Mol Sci 2010;11(5):2188–99.
[45] Ruela-de-Sousa RR, Fuhler G M, Blom N, Ferreira CV, Aoyama H, Peppelenbosch M P, et al. Cytotoxicity of apigenin on leukemia cell lines: implications for prevention and therapy. Cell Death Dis 2010;1(1):e19.
[46] Ujiki MB, Ding X Z, Salabat M R, Bentrem D J, Golkar L, Milam B, et al. Apigenin inhibits pancreatic cancer cell proliferation through G2/M cell cycle arrest. Mol Cancer 2006;5(1):1–8.
[47] Panche A, Diwan A, Chandra S. Flavonoids: an overview. J Nutr Sci 2016;5:1–15.
[48] Pietta P-G. Flavonoids as antioxidants. J Nat Products 2000;63(7):1035–42.
[49] Ribeiro D, Freitas M, Tomé S M, Silva A, Laufer S, Lima J L, et al. Flavonoids inhibit COX-1 and COX-2 enzymes and cytokine/chemokine production in human whole blood. Inflammation 2015;38(2):858–70.
[50] Rice-Evans C. Flavonoid antioxidants. Curr Med Chem 2001;8(7):797–807.
[51] Schubert SY, Lansky EP, Neeman I. Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids. J Ethnopharmacol 1999;66(1):11–17.
[52] Wang C, Mäkelä T, Hase T, Adlercreutz H, Kurzer M S, et al. Lignans and flavonoids inhibit aromatase enzyme in human preadipocytes. J Steroid Biochem Mol Biol 1994;50(3–4):205–12.
[53] Lin C-M, Chen C S, Chen C T, Liang Y C, Lin J K, et al. Molecular modeling of flavonoids that inhibits xanthine oxidase. Biochem Biophys Res Commun 2002;294(1):167–72.
[54] Lin S, Zhang G, Liao Y, Pan J, Gong D, et al. Dietary flavonoids as xanthine oxidase inhibitors: Structure–affinity and structure–activity relationships. J Agric Food Chem, 2015;63(35):7784–94.
[55] Enroth C, Eger B T, Okamoto K, Nishino T, Nishino T, Pai E F, et al. Crystal structures of bovine milk xanthine dehydrogenase and xanthine oxidase: structure-based mechanism of conversion. In: Proceedings of the National Academy of Sciences, USA. 97; 2000. p. 10723–8.
[56] Beiler J, Martin GJ. The inhibition of xanthine oxidase by flavonoids and related compounds. J. Biol. Chem 1951;192(2):831–4.
[57] Dong Y, Huang H, Zhao M, Sun-Waterhouse D, Lin L, Xiao C, et al. Mechanisms underlying the xanthine oxidase inhibitory effects of dietary flavonoids galangin and pinobanksin. J Funct Foods 2016;24:26–36.
[58] Lin J-K, Tsai S-H, Lin-Shiau S-Y. Antiinflammatory and antitumor effects of flavonoids and flavanoids. Drugs Future 2001;26(2):145–52.
[59] Ponce AM, Blanco S E, Molina A S, García-Domenech R, Gálvez J, et al. Study of the action of flavonoids on xanthine-oxidase by molecular topology. J Chem Inf Comp Sci 2000;40(4):1039–45.
[60] Shi Y, Williamson G. Quercetin lowers plasma uric acid in pre-hyperuricaemic males: a randomized, double-blinded, placebo-controlled, cross-over trial. Br J Nutr 2016;115(5):800–6.
[61] Miles SL, McFarland M, Niles RM. Molecular and physiological actions of quercetin: need for clinical trials to assess its benefits in human disease. Nutr Rev 2014;72(11):720–34.
[62] Zhu JX, Wang Y, Kong L D, Yang C, Zhang X, et al. Effects of Biota orientalis extract and its flavonoid constituents, quercetin and rutin on serum uric acid levels in oxonate-induced mice and xanthine dehydrogenase and xanthine oxidase activities in mouse liver. J Ethnopharmacol 2004;93(1):133–40.
[63] de Souza MR, de Paula C A, de Resende M L P, Grabe-Guimarães A, de Souza Filho J D, Saúde-Guimarães D A, et al. Pharmacological basis for use of Lychnophora trichocarpa in gouty arthritis: anti-hyperuricemic and anti-inflammatory effects of its extract, fraction and constituents. J Ethnopharmacol 2012;142(3):845–50.
[64] Huang J, Wang S, Zhu M, Chen J, Zhu X, et al. Effects of genistein, apigenin, quercetin, rutin and astilbin on serum uric acid levels and xanthine oxidase activities in normal and hyperuricemic mice. Food Chem Toxicol 2011;49(9):1943–7.
[65] Ahmad NS, Farman M, Najmi M H, Mian K B, Hasan A, et al. Pharmacological basis for use of Pistacia integerrima leaves in hyperuricemia and gout. J Ethnopharmacol 2008;117(3):478–82.
[66] Mo S-F, Zhou F, Lv Y Z, Hu Q H, Zhang D M, Kong L D, et al. Hypouricemic action of selected flavonoids in mice: structure–activity relationships. Biol Pharm Bull 2007;30(8):1551–6.
[67] Derosa G, D'Angelo A, Maffioli P. Evaluation of the effects of a supplement composed by quercetin, rutin, bromelain and L-carnosine in patients with borderline uricemia. J Food Nutr Res 2020;8(10):550–5.
[68] Shukla S, Gupta S. Apigenin: a promising molecule for cancer prevention. Pharm Res 2010;27(6):962–78.
[69] Shukla S, Gupta S. Apigenin: a promising molecule for cancer prevention. Pharm Res 2010;27(6):962–78.
[70] Flemmig J, Kuchta K, Arnhold J, Rauwald H W, et al. Olea europaea leaf (Ph. Eur.) extract as well as several of its isolated phenolics inhibit the gout-related enzyme xanthine oxidase. Phytomedicine 2011;18(7):561–6.
[71] Shin G-C, Kim C, Lee J M, Cho W S, Lee S G, Jeong M, et al. Apigenin-induced apoptosis is mediated by reactive oxygen species and activation of ERK1/2 in rheumatoid fibroblast-like synoviocytes. Chem Biol Interact 2009;182(1):29–36.
[72] Mak P, Leung Y K, Tang W Y, Harwood C, Ho S M, et al. Apigenin suppresses cancer cell growth through ERβ. Neoplasia 2006;8(11):896–904.
[73] Chen D, Landis-Piwowar K R, Chen M S, Dou Q P, et al. Inhibition of proteasome activity by the dietary flavonoid apigenin is associated with growth inhibition in cultured breast cancer cells and xenografts. Breast Cancer Res 2007;9(6):R80.
[74] Way T-D, Kao M-C, Lin J-K. Degradation of HER2/neu by apigenin induces apoptosis through cytochrome c release and caspase-3 activation in HER2/neu-overexpressing breast cancer cells. Febs Lett 2005;579(1):145–52.
[75] Weldon CB, McKee A, Collins-Burow B M, Melnik L I, Scandurro A B, McLachlan J A, et al. PKC-mediated survival signaling in breast carcinoma cells: a role for MEK1-AP1 signaling. Int J Oncol 2005;26(3):763–8.
[76] Liu LZ, Fang J, Zhou Q, Hu X, Shi X, Jiang B H, et al. Apigenin inhibits expression of vascular endothelial growth factor and angiogenesis in human lung cancer cells: implication of chemoprevention of lung cancer. Mol Pharmacol 2005;68(3):635–43.
[77] Chen M, Wang X, Zha D, Cai F, Zhang W, He Y, et al. Apigenin potentiates TRAIL therapy of non-small cell lung cancer via upregulating DR4/DR5 expression in a p53-dependent manner. Sci Rep 2016;6(1):1–17.
[78] Dai J, Van Wie P G, Fai L Y, Kim D, Wang L, Poyil P, et al. Downregulation of NEDD9 by apigenin suppresses migration, invasion, and metastasis of colorectal cancer cells. Toxicol Appl Pharmacol 2016;311:106–12.
[79] Banerjee K, Mandal M. Oxidative stress triggered by naturally occurring flavone apigenin results in senescence and chemotherapeutic effect in human colorectal cancer cells. Redox Biol 2015;5:153–62.
[80] Xu M, Wang S, Song Y U, Yao J, Huang K, Zhu X, et al. Apigenin suppresses colorectal cancer cell proliferation, migration and invasion via inhibition of the Wnt/β-catenin signaling pathway. Oncol Lett 2016;11(5):3075–80.
[81] Zheng P-W, Chiang L-C, Lin C-C. Apigenin induced apoptosis through p53-dependent pathway in human cervical carcinoma cells. Life Sci 2005;76(12):1367–79.
[82] Erdogan S, Doganlar O, Doganlar Z B, Serttas R, Turkekul K, Dibirdik I, et al. The flavonoid apigenin reduces prostate cancer CD44+ stem cell survival and migration through PI3K/Akt/NF-κB signaling. Life Sci 2016;162:77–86.
[83] Shukla S, Kanwal R, Shankar E, Datt M, Chance M R, Fu P, et al. Apigenin blocks IKKα activation and suppresses prostate cancer progression. Oncotarget 2015;6(31):31216.
[84] Zhu Y, Wu J, Li S, Wang X, Liang Z, Xu X, et al. Apigenin inhibits migration and invasion via modulation of epithelial mesenchymal transition in prostate cancer. Mol Med Rep 2015;11(2):1004–8.
[85] Gómez-García FJ, López-Jornet M P, Álvarez-Sánchez N, Castillo-Sánchez J, Benavente-García O, Vicente Ortega V, et al. Effect of the phenolic compounds apigenin and carnosic acid on oral carcinogenesis in hamster induced by DMBA. Oral Dis 2013;19(3):279–86.
[86] Maggioni D, Garavello W, Rigolio R, Pignataro L, Gaini R, Nicolini G, et al. Apigenin impairs oral squamous cell carcinoma growth in vitro inducing cell cycle arrest and apoptosis. Int J Oncol 2013;43(5):1675–82.
[87] Imran M, Aslam Gondal T, Atif M, Shahbaz M, Batool Qaisarani T, Hanif Mughal M, et al. Apigenin as an anticancer agent. Phytother Res 2020;34(8):1812–28.
[88] Bridgeman BB, Wang P, Ye B, Pelling J C, Volpert O V, Tong X, et al. Inhibition of mTOR by apigenin in UVB-irradiated keratinocytes: a new implication of skin cancer prevention. Cell Signal 2016;28(5):460–8.
[89] Chen J, Chen J, Li Z, Liu C, Yin L, et al. The apoptotic effect of apigenin on human gastric carcinoma cells through mitochondrial signal pathway. Tumor Biol 2014;35(8):7719–26.
[90] Liu X, Li L, Lv L, Chen D, Shen L, Xie Z, et al. Apigenin inhibits the proliferation and invasion of osteosarcoma cells by suppressing the Wnt/β-catenin signaling pathway. Oncol Rep 2015;34(2):1035–41.
[91] Das A, Banik NL, Ray SK. Flavonoids activated caspases for apoptosis in human glioblastoma T98G and U87MG cells but not in human normal astrocytes. Cancer 2010;116(1):164–76.
[92] Hu XY, Liang J Y, Guo X J, Liu L, Guo Y B, et al. 5-Fluorouracil combined with apigenin enhances anticancer activity through mitochondrial membrane potential ($\Delta\Psi$m)-mediated apoptosis in hepatocellular carcinoma. Clin Exp Pharmacol Physiol 2015;42(2):146–53.
[93] Jayasooriya RGPT, Kang SH, Kang CH, Choi YH, Moon DO, Hyun JW, et al. Apigenin decreases cell viability and telomerase activity in human leukemia cell lines. Food Chem Toxicol 2012;50(8):2605–11.
[94] Worachartcheewan A, Nantasenamat C, Isarankura-Na-Ayudhya C, Prachayasittikul V, et al. Probing the origins of anticancer activity of chrysin derivatives. Med Chem Res 2015;24(5):1884–92.
[95] Woo KJ, Jeong Y J, Inoue H, Park J W, Kwon T K, et al. Chrysin suppresses lipopolysaccharide-induced cyclooxygenase-2 expression through the inhibition of nuclear factor for IL-6 (NF-IL6) DNA-binding activity. FEBS letters 2005;579(3):705–11.
[96] Ojha R, Singh J, Ojha A, Singh H, Sharma S, Nepali K, et al. An updated patent review: xanthine oxidase inhibitors for the treatment of hyperuricemia and gout (2011-2015). Expert Opin Ther Pat 2017;27(3):311–45.

[97] Samarghandian S, Afshari JT, Davoodi S. Chrysin reduces proliferation and induces apoptosis in the human prostate cancer cell line pc-3. Clinics (Sao Paulo) 2011;66(6):1073–9.
[98] Fu B, Xue J, Li Z, Shi X, Jiang B H, Fang J, et al. Chrysin inhibits expression of hypoxia-inducible factor-1α through reducing hypoxia-inducible factor-1α stability and inhibiting its protein synthesis. Mol Cancer Ther 2007;6(1):220–6.
[99] Wu YX, Fang X. Apigenin, chrysin, and luteolin selectively inhibit chymotrypsin-like and trypsin-like proteasome catalytic activities in tumor cells. Planta Med 2010;76(2):128–32.
[100] Li X, Huang Q, Ong C N, Yang X F, Shen H M, et al. Chrysin sensitizes tumor necrosis factor-α-induced apoptosis in human tumor cells via suppression of nuclear factor-kappaB. Cancer Lett 2010;293(1):109–16.
[101] Li-Weber M. Targeting apoptosis pathways in cancer by Chinese medicine. Cancer Lett 2013;332(2):304–12.
[102] Woo KJ, Yoo Y H, Park J W, Kwon T K, et al. Bcl-2 attenuates anticancer agents-induced apoptosis by sustained activation of Akt/protein kinase B in U937 cells. Apoptosis 2005;10(6):1333–43.
[103] Cogulu O, Biray C, Gunduz C, Karaca E, Aksoylar S, Sorkun K, Salih B, Ozkinay F, et al. Effects of Manisa propolis on telomerase activity in leukemia cells obtained from the bone marrow of leukemia patients. Int J Food Sci Nutr 2009;60(7):601–5.
[104] Zhang Q, Zhao XH, Wang ZJ. Cytotoxicity of flavones and flavonols to a human esophageal squamous cell carcinoma cell line (KYSE-510) by induction of G2/M arrest and apoptosis. Toxicol In Vitro 2009;23(5):797–807.
[105] Sun LP, Chen A L, Hung H C, Chien Y H, Huang J S, Huang C Y, et al. Chrysin: a histone deacetylase 8 inhibitor with anticancer activity and a suitable candidate for the standardization of Chinese propolis. J Agric Food Chem 2012;60(47):11748–58.
[106] Samarghandian S, Azimi-Nezhad M, Borji A, Hasanzadeh M, Jabbari F, Farkhondeh T, et al. Inhibitory and cytotoxic activities of chrysin on human breast adenocarcinoma cells by induction of apoptosis. Pharmacogn Mag 2016;12(Suppl 4):S436.
[107] Zhang T, Chen X, Qu L, Wu J, Cui R, Zhao Y, et al. Chrysin and its phosphate ester inhibit cell proliferation and induce apoptosis in Hela cells. Bioorg Med Chem 2004;12(23):6097–105.
[108] Karthikeyan S, Srinivasan R, Wani S A, Manoharan S, et al. Chemopreventive potential of chrysin in 7, 12-dimethylbenz (a)anthracene-induced hamster buccal pouch carcinogenesis. International Journal of Nutrition. Pharmacol Neurol Dis 2013;3(1):46.
[109] Prabhakar MM, Manoharan S, Baskaran N, Srinivasan R, Karthikeyan S, Wani S A, et al. Chemopreventive potential of chrysin in 7, 12-dimethylbenz (a) anthracene induced skin carcinogenesis in Swiss albino mice. Int J Pharm Sci 2012;3:89–96.
[110] Srinivasan R, Manoharan S. Chemopreventive Potential of Chrysin in 7, 12-dimethylbenz (A) anthracene induced mammary carcinogenesis in sprague-dawley rats. J Cell Tissue Res 2011;11(3):2909.
[111] Miyamoto S, Yasui Y, Ohigashi H, Tanaka T, Murakami A, et al. Dietary flavonoids suppress azoxymethane-induced colonic preneoplastic lesions in male C57BL/KsJ-db/db mice. Chem Biol Interac 2010;183(2):276–83.
[112] Samarghandian S, Nezhad MAzimi, Mohammadi G. Role of caspases, Bax and Bcl-2 in chrysin-induced apoptosis in the A549 human lung adenocarcinoma epithelial cells. Anticancer Agents Med Chem 2014;14(6):901–9.
[113] Maasomi ZJ, Soltanahmadi Y P, Dadashpour M, Alipour S, Abolhasani S, Zarghami N, et al. Synergistic anticancer effects of silibinin and chrysin in T47D breast cancer cells. Asian Pac J Cancer Prev 2017;18(5):1283.
[114] Kim SH, Choi KC. Anti-cancer effect and underlying mechanism(s) of kaempferol, a phytoestrogen, on the regulation of apoptosis in diverse cancer cell models. Toxicol Res 2013;29(4):229–34.
[115] Lau T. A healthy way to live: the occurrence, bioactivity, biosynthesis and synthesis of kaempferol. Chemistry 2008;150:1–3.
[116] Haidari F, Keshavarz S A, Shahi M M, Mahboob S A, Rashidi M R, et al. Effects of parsley (Petroselinum crispum) and its Flavonol constituents, Kaempferol and Quercetin, on serum uric acid levels, biomarkers of oxidative stress and liver xanthine oxidoreductase aactivity inoxonate-induced hyperuricemic rats. Iran J Pharm Res 2011;10(4):811.
[117] Wang Y, Zhang G, Pan J, Gong D, et al. Novel insights into the inhibitory mechanism of kaempferol on xanthine oxidase. J Agric Food Chem 2015;63(2):526–34.
[118] Chen H-J, Lin C M, Lee C Y, Shih N C, Peng S F, Tsuzuki M, et al. Kaempferol suppresses cell metastasis via inhibition of the ERK-p38-JNK and AP-1 signaling pathways in U-2 OS human osteosarcoma cells. Oncol Rep 2013;30(2):925–32.
[119] Jaramillo-Carmona S, Lopez S, Abia R, Rodriguez-Arcos R, Jimenez A, Guillen R, et al. Combination of quercetin and kaempferol enhances in vitro cytotoxicity on human colon cancer (HCT-116) cells. Rec Nat Prod 2014;8(3):262.
[120] Sharma V, Joseph C, Ghosh S, Agarwal A, Mishra M K, Sen E, et al. Kaempferol induces apoptosis in glioblastoma cells through oxidative stress. Mol Cancer Ther 2007;6(9):2544–53.
[121] Song W, Dang Q, Xu D, Chen Y, Zhu G, Wu K, et al. Kaempferol induces cell cycle arrest and apoptosis in renal cell carcinoma through EGFR/p38 signaling. Oncol Rep 2014;31(3):1350–6.
[122] Wu P, Meng X, Zheng H, Zeng Q, Chen T, Wang W, et al. Kaempferol attenuates ROS-induced hemolysis and the molecular mechanism of its induction of apoptosis on bladder cancer. Molecules 2018;23(10):2592.
[123] Zhang Y, Chen A Y, Li M, Chen C, Yao Q, et al. Ginkgo biloba extract kaempferol inhibits cell proliferation and induces apoptosis in pancreatic cancer cells. J Surg Res 2008;148(1):17–23.
[124] Wang J, Fang F, Huang Z, Wang Y, Wong C, et al. Kaempferol is an estrogen-related receptor α and γ inverse agonist. FEBS letters 2009;583(4):643–7.
[125] Kalyani, C.N., ML.; Devi, Y.P, Effect of phytochemical kaempferol on HCT-15 and lymphocytes Indian J Appl Res, 2015. 5(10): p. 452-454.
[126] Alenzi FQ, Lotfy M, Wyse R. Swords of cell death: caspase activation and regulation. Asian Pac J Cancer Prev 2010;11(2):271–80.
[127] Kang GY, Lee E R, Kim J H, Jung J W, Lim J, Kim S K, et al. Downregulation of PLK-1 expression in kaempferol-induced apoptosis of MCF-7 cells. Eur J Pharmacol 2009;611(1–3):17–21.
[128] Luo H, Rankin G O, Liu L, Daddysman M K, Jiang B H, Chen Y C, et al. Kaempferol inhibits angiogenesis and VEGF expression through both HIF dependent and independent pathways in human ovarian cancer cells. Nutr Cancer 2009;61(4):554–63.
[129] Luo H, Jiang B, Li B, Li Z, Jiang B H, Chen Y C, et al. Kaempferol nanoparticles achieve strong and selective inhibition of ovarian cancer cell viability. Int J Nanomed 2012;7:3951.
[130] Jo E, Park S J, Choi Y S, Jeon W K, Kim B C, et al. Kaempferol suppresses transforming growth factor-β1–induced epithelial-to-mesenchymal transition and migration of A549 lung cancer cells by inhibiting Akt1-mediated phosphorylation of Smad3 at threonine-179. Neoplasia 2015;17(7):525–37.
[131] Khantamat O, Chaiwangyen W, Limtrakul P-n. Screening of flavonoids for their potential inhibitory effect on P-glycoprotein activity in human cervical carcinoma KB cells. Chiang Mai Medical Journal-เชียงใหม่ เวช สาร 2004;43(2):45–56.
[132] Colombo M, Figueiró F, de Fraga Dias A, Teixeira HF, Battastini AMO, Koester L S, et al. Kaempferol-loaded mucoadhesive nanoemulsion for intranasal administration reduces glioma growth in vitro. Int J Pharm 2018;543(1–2):214–23.
[133] Jeong JC, Kim M S, Kim T H, Kim Y K, et al. Kaempferol induces cell death through ERK and Akt-dependent down-regulation of XIAP and survivin in human glioma cells. Neurochem Res 2009;34(5):991–1001.
[134] Mylonis I, Lakka A, Tsakalof A, Simos G, et al. The dietary flavonoid kaempferol effectively inhibits HIF-1 activity and hepatoma cancer cell viability under hypoxic conditions. Biochem Biophys Res Commun 2010;398(1):74–8.
[135] Seydi E, Salimi A, Rasekh H R, Mohsenifar Z, Pourahmad J, et al. Selective cytotoxicity of luteolin and kaempferol on cancerous hepatocytes obtained from rat model of hepatocellular carcinoma: involvement of ROS-mediated mitochondrial targeting. Nutr Cancer 2018;70(4):594–604.
[136] Zhu G, Liu X, Li H, Yan Y, Hong X, Lin Z, et al. Kaempferol inhibits proliferation, migration, and invasion of liver cancer HepG2 cells by down-regulation of microRNA-21. Int J Immunopathol Pharmacol 2018;32:2058738418814341.
[137] Bandyopadhyay S, Romero JR, Chattopadhyay N. Kaempferol and quercetin stimulate granulocyte-macrophage colony-stimulating factor secretion in human prostate cancer cells. Mol Cell Endocrinol 2008;287(1-2):57–64.
[138] Kang JW, Kim J H, Song K, Kim S H, Yoon J H, Kim K S, et al. Kaempferol and quercetin, components of Ginkgo biloba extract (EGb 761), induce caspase-3-dependent apoptosis in oral cavity cancer cells. Phytother Res 2010;24(S1):S77–82.
[139] Li R, Mei J, Liu G. Kaempferol-induced apoptosis of human esophageal squamous carcinoma Eca-109 cells and the mechanism. J South Med Univ 2011;31(8):1440–2.
[140] Lin C-W, Chen P N, Chen M K, Yang W E, Tang C H, Yang S F, et al. Kaempferol reduces matrix metalloproteinase-2 expression by down-regulating ERK1/2 and the activator protein-1 signaling pathways in oral cancer cells. PLoS One 2013;8(11):e80883.
[141] Yao S, Wang X, Li C, Zhao T, Jin H, Fang W, et al. Kaempferol inhibits cell proliferation and glycolysis in esophagus squamous cell carcinoma via targeting EGFR signaling pathway. Tumor Biol 2016;37(8):10247–56.
[142] Lopez-Lazaro M. Distribution and biological activities of the flavonoid luteolin. Mini Rev Med Chem 2009;9(1):31–59.
[143] Irondi EA, Agboola S O, Oboh G, Boligon A A, Athayde M L, Shode F O, et al. Guava leaves polyphenolics-rich extract inhibits vital enzymes implicated in gout and hypertension in vitro. J Intercult Ethnopharmacol 2016;5(2):122.
[144] Yan J, Zhang G, Hu Y, Ma Y, et al. Effect of luteolin on xanthine oxidase: Inhibition kinetics and interaction mechanism merging with docking simulation. Food Chem 2013;141(4):3766–73.
[145] Arnold RS, Shi J, Murad E, Whalen A M, Sun C Q, Polavarapu R, et al. Hydrogen peroxide mediates the cell growth and transformation caused by the mitogenic oxidase Nox1. Proc Natl Acad Sci U S A 2001;98(10):5550–5.
[146] Church SL, Grant J W, Ridnour L A, Oberley L W, Swanson P E, Meltzer P S, et al. Increased manganese superoxide dismutase expression suppresses the malignant phenotype of human melanoma cells. Proc Natl Acad Sci USA, 1993;90(7):3113–17.

[147] Leung HWC, Kuo C L, Yang W H, Lin C H, Lee H Z, et al. Antioxidant enzymes activity involvement in luteolin-induced human lung squamous carcinoma CH27 cell apoptosis. Eur J Pharmacol 2006;534(1–3):12–18.
[148] Zhang Y, Zhao W, Zhang H J, Domann F E, Oberley L W, et al. Overexpression of copper zinc superoxide dismutase suppresses human glioma cell growth. Cancer Res 2002;62(4):1205–12.
[149] Chiu FL, Lin JK. Downregulation of androgen receptor expression by luteolin causes inhibition of cell proliferation and induction of apoptosis in human prostate cancer cells and xenografts. Prostate 2008;68(1):61–71.
[150] Han K, Meng W, Zhang J J, Zhou Y, Wang YL, Su Y, et al. Luteolin inhibited proliferation and induced apoptosis of prostate cancer cells through miR-301. OncoTargets Ther 2016;9:3085.
[151] Pratheeshkumar P, Son Y O, Budhraja A, Wang X, Ding S, Wang L, et al. Luteolin inhibits human prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. PloS one 2012;7(12):e52279.
[152] Gray AL, Stephens C A, Bigelow R L, Coleman D T, Cardelli J A, et al. The polyphenols (−)-epigallocatechin-3-gallate and luteolin synergistically inhibit TGF-β-induced myofibroblast phenotypes through RhoA and ERK inhibition. PLoS One 2014;9(10):e109208.
[153] Sakurai MA, Ozaki Y, Okuzaki D, Naito Y, Sasakura T, Okamoto A, et al. Gefitinib and luteolin cause growth arrest of human prostate cancer PC-3 cells via inhibition of cyclin G-associated kinase and induction of miR-630. PloS one 2014;9(6):e100124.
[154] Tsai P-H, Cheng C H, Lin C Y, Huang Y T, Lee L T, Kandaswami C C, et al. Dietary flavonoids luteolin and quercetin suppressed cancer stem cell properties and metastatic potential of isolated prostate cancer cells. Anticancer Res 2016;36(12):6367–80.
[155] Shi R-X, Ong C-N, Shen H-M. Luteolin sensitizes tumor necrosis factor-α-induced apoptosis in human tumor cells. Oncogene 2004;23(46):7712.
[156] Ashokkumar P, Sudhandiran G. Luteolin inhibits cell proliferation during azoxymethane-induced experimental colon carcinogenesis via Wnt/β-catenin pathway. Invest New Drugs 2011;29(2):273–84.
[157] Pandurangan AK, Dharmalingam P, Sadagopan S KA, Ganapasam S, et al. Luteolin inhibits matrix metalloproteinase 9 and 2 in azoxymethane-induced colon carcinogenesis. Hum Exp Toxicol 2014;33(11):1176–85.
[158] Pandurangan AK, Kumar SAS, Dharmalingam P, Ganapasam S, et al. Luteolin, a bioflavonoid inhibits azoxymethane-induced colon carcinogenesis: involvement of iNOS and COX-2. Pharmacogn Mag 2014;10(Suppl 2):S306.
[159] Cai X, Ye T, Liu C, Lu W, Lu M, Zhang J, et al. Luteolin induced G2 phase cell cycle arrest and apoptosis on non-small cell lung cancer cells. Toxicol In Vitro 2011;25(7):1385–91.
[160] Yang G, Wang Z, Wang W, Zhou X, Hu X, Yang J, et al. Anticancer activity of luteolin and its synergism effect with BCG on human bladder cancer cell line BIU-87. J Cent SouthUniv 2014;39(4):371–8.
[161] Yan J, Wang Q, Zheng X, Sun H, Zhou Y, Li D, et al. Luteolin enhances TNF-related apoptosis-inducing ligand's anticancer activity in a lung cancer xenograft mouse model. Biochem Biophys Res Commun 2012;417(2):842–6.
[162] Yoo DR, Jang Y H, Jeon Y K, Kim J Y, Jeon W, Choi Y J, et al. Proteomic identification of anti-cancer proteins in luteolin-treated human hepatoma Huh-7 cells. Cancer Lett 2009;282(1):48–54.
[163] Attoub S, Hassan AH, Vanhoecke B, Iratni R, Takahashi T, Gaben A M, et al. Inhibition of cell survival, invasion, tumor growth and histone deacetylase activity by the dietary flavonoid luteolin in human epithelioid cancer cells. Eur J Pharmacol 2011;651(1–3):18–25.
[164] Samy RP, Gopalakrishnakone P, Ignacimuthu S. Anti-tumor promoting potential of luteolin against 7,12-dimethylbenz(a)anthracene-induced mammary tumors in rats. Chem Biol Interact 2006;164(1-2):1–14.
[165] Selvendiran K, Koga H, Ueno T, Yoshida T, Maeyama M, Torimura T, et al. Luteolin promotes degradation in signal transducer and activator of transcription 3 in human hepatoma cells: an implication for the antitumor potential of flavonoids. Cancer Res 2006;66(9):4826–34.
[166] Sui J-Q, Xie K-P, Xie M-J. Inhibitory effect of luteolin on the proliferation of human breast cancer cell lines induced by epidermal growth factor. Sheng li xue bao:[Acta physiologica Sinica] 2016;68(1):27–34.
[167] Tu D-G, Lin W T, Yu C C, Lee S S, Peng C Y, Lin T, et al. Chemotherapeutic effects of luteolin on radio-sensitivity enhancement and interleukin-6/signal transducer and activator of transcription 3 signaling repression of oral cancer stem cells. J Formos Med Assoc 2016;115(12):1032–8.
[168] Yang S-F, Yang W E, Chang H R, Chu S C, Hsieh Y S, et al. Luteolin induces apoptosis in oral squamous cancer cells. J Dent Res 2008;87(4):401–6.
[169] Selvi RB, Swaminathan A, Chatterjee S, Shanmugam M K, Li F, Ramakrishnan G B, et al. Inhibition of p300 lysine acetyltransferase activity by luteolin reduces tumor growth in head and neck squamous cell carcinoma (HNSCC) xenograft mouse model. Oncotarget 2015;6(41):43806.
[170] Ding S, Hu A, Hu Y, Ma J, Weng P, Dai J, et al. Anti-hepatoma cells function of luteolin through inducing apoptosis and cell cycle arrest. Tumor Biol 2014;35(4):3053–60.
[171] Hwang J-T, Park O J, Lee Y K, Sung M J, Hur H J, Kim M S, et al. Anti-tumor effect of luteolin is accompanied by AMP-activated protein kinase and nuclear factor-κB modulation in HepG2 hepatocarcinoma cells. Int J Mol Med 2011;28(1):25–31.
[172] Lee W-J, Wu L F, Chen W K, Wang C J, Tseng T H, et al. Inhibitory effect of luteolin on hepatocyte growth factor/scatter factor-induced HepG2 cell invasion involving both MAPK/ERKs and PI3K–Akt pathways. Chem Biol Interact 2006;160(2):123–33.
[173] Xu H, Yang T, Liu X, Tian Y, Chen X, Yuan R, et al. Luteolin synergizes the antitumor effects of 5-fluorouracil against human hepatocellular carcinoma cells through apoptosis induction and metabolism. Life Sci 2016;144:138–47.
[174] Yee SB, Choi H J, Chung S W, Park D H, Sung B, Chung H Y, et al. Growth inhibition of luteolin on HepG2 cells is induced via p53 and Fas/Fas-ligand besides the TGF-β pathway. Int J Oncol 2015;47(2):747–54.
[175] Imran M, Rauf A, Abu-Izneid T, Nadeem M, Shariati M A, Khan I A, et al. Luteolin, a flavonoid, as an anticancer agent: a review. Biomed Pharmacother 2019;112:108612.
[176] Chen J, Kang J, Da W, Ou Y, et al. Combination with water-soluble antioxidants increases the anticancer activity of quercetin in human leukemia cells. Pharmazie 2004;59(11):859–63.
[177] Joshi UJ, Gadge A S, D'Mello P, Sinha R, Srivastava S, Govil G, et al. Anti-inflammatory, antioxidant and anticancer activity of quercetin and its analogues. Int J Res Pharma Biomed Sci 2011;2:1756–66.
[178] Boly R, Gras T, Lamkami T, Guissou P, Serteyn D, Kiss R, et al. Quercetin inhibits a large panel of kinases implicated in cancer cell biology. Int J Oncol 2011;38(3):833–42.
[179] Chen J, Kang JH. Quercetin and trichostatin A cooperatively kill human leukemia cells. Pharmazie 2005;60(11):856–60.
[180] Tao, S.-f., H.-f. He, and Q. Chen, Quercetin inhibits proliferation and invasion acts by up-regulating miR-146a in human breast cancer cells. Mol Cell Biochem, 2015. 402(1): p. 93-100.
[181] Seo H-S, Ku J M, Choi H S, Choi Y K, Woo J K, Kim M, et al. Quercetin induces caspase-dependent extrinsic apoptosis through inhibition of signal transducer and activator of transcription 3 signaling in HER2-overexpressing BT-474 breast cancer cells. Oncol Rep 2016;36(1):31–42.
[182] Niu G, Yin S, Xie S, Li Y, Nie D, Ma L, et al. Quercetin induces apoptosis by activating caspase-3 and regulating Bcl-2 and cyclooxygenase-2 pathways in human HL-60 cells. Acta Biochim Biophys Sin (Shanghai) 2011;43(1):30–7.
[183] Brisdelli F, Bennato F, Bozzi A, Cinque B, Mancini F, Iorio R, et al. ELF-MF attenuates quercetin-induced apoptosis in K562 cells through modulating the expression of Bcl-2 family proteins. Mol Cell Biochem 2014;397(1):33–43.
[184] Chen X, Dong X S, Gao H Y, Jiang Y F, Jin Y L, Chang Y Y, et al. Suppression of HSP27 increases the anti–tumor effects of quercetin in human leukemia U937 cells. Mol Med Rep 2015;13(1):689–96.
[185] Chen FY, Cao L F, Wan H X, Zhang M Y, Cai J Y, Shen L J, et al. Quercetin enhances adriamycin cytotoxicity through induction of apoptosis and regulation of mitogen–activated protein kinase/extracellular signal–regulated kinase/c–Jun N–terminal kinase signaling in multidrug–resistant leukemia K562 cells. Mol Med Rep 2015;11(1):341–8.
[186] Maso V, Calgarotto A K, Franchi G C, Nowill A E, Vassallo J, Saad STO, et al. Multitarget effects of quercetin in leukemia. Cancer Prev Res 2014;7(12):1240–50.
[187] Xing N, Chen Y, Mitchell S H, Young C Y, et al. Quercetin inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. Carcinogenesis 2001;22(3):409–14.
[188] Linsalata M, Orlando A, Messa C, Refolo M G, Russo F, et al. Quercetin inhibits human DLD-1 colon cancer cell growth and polyamine biosynthesis. Anticancer Res 2010;30(9):3501–7.
[189] Ren MX, Deng X H, Ai F, Yuan G Y, Song H Y, et al. Effect of quercetin on the proliferation of the human ovarian cancer cell line SKOV-3 in vitro. Exp Ther Med 2015;10(2):579–83.
[190] Han M, Song Y, Zhang X. Quercetin suppresses the migration and invasion in human colon cancer Caco-2 cells through regulating toll-like receptor 4/nuclear factor-kappa B pathway. Pharmacogn Mag 2016;12(Suppl 2):S237.
[191] Kee J-Y, Han Y H, Kim D S, Mun J G, Park J, Jeong M Y, et al. Inhibitory effect of quercetin on colorectal lung metastasis through inducing apoptosis, and suppression of metastatic ability. Phytomedicine 2016;23(13):1680–90.
[192] Maurya AK, Vinayak M. Anticarcinogenic action of quercetin by downregulation of phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC) via induction of p53 in hepatocellular carcinoma (HepG2) cell line. Mol Biol Rep 2015;42(9):1419–29.
[193] Zhao P, Mao J M, Zhang S Y, Zhou Z Q, Tan Y, Zhang Y, et al. Quercetin induces HepG2 cell apoptosis by inhibiting fatty acid biosynthesis. Oncol Lett 2014;8(2):765–9.
[194] Zheng S-Y, Li Y, Jiang D, Zhao J, Ge J F, et al. Anticancer effect and apoptosis induction by quercetin in the human lung cancer cell line A-549. Mol Med Rep 2012;5(3):822–6.
[195] Xingyu Z, Peijie M, Dan P, Youg W, Daojun W, Xinzheng C, et al. Quercetin suppresses lung cancer growth by targeting Aurora B kinase. Cancer Med 2016;5(11):3156–65.
[196] Berndt K, Campanile C, Muff R, Strehler E, Born W, Fuchs B, et al. Evaluation of quercetin as a potential drug in osteosarcoma treatment. Anticancer Res 2013;33(4):1297–306.
[197] Zhang X, Guo Q, Chen J, Chen Z, et al. Quercetin enhances cisplatin sensitivity of human osteosarcoma cells by modulating microRNA-217-KRAS axis. Mol Cells 2015;38(7):638.
[198] Liang W, Li X, Li C, Liao L, Gao B, Gan H, et al. Quercetin-mediated apoptosis via activation of the mitochondrial-dependent pathway in MG-63 osteosarcoma cells. Mol Med Rep 2011;4(5):1017–23.

[199] Li J, Tang C, Li L, Li R, Fan Y, et al. Quercetin sensitizes glioblastoma to t-AUCB by dual inhibition of Hsp27 and COX-2 in vitro and in vivo. J Exp Clin Cancer Res 2016;35(1):1–11.
[200] Park MH. Quercetin-induced downregulation of phospholipase D1 inhibits proliferation and invasion in U87 glioma cells. Biochem Biophys Res Commun 2011;412(4):710–15.
[201] Wang H, Yuan Z, Chen Z, Yao F, Hu Z, Wu B, et al. Effect of quercetin on glioma cell U87 apoptosis and feedback regulation of MDM2-p53. Nan fang yi ke da xue xue bao=. J South Med Univ 2014;34(5):686–9.
[202] Del Follo-Martinez A, Banerjee N, Li X, Safe S, Mertens-Talcott S, et al. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Nutr Cancer 2013;65(3):494–504.
[203] Sharma V, Kumar L, Mohanty S K, Maikhuri J P, Rajender S, Gupta G, et al. Sensitization of androgen refractory prostate cancer cells to anti-androgens through re-expression of epigenetically repressed androgen receptor–synergistic action of quercetin and curcumin. Mol Cell Endocrinol 2016;431:12–23.
[204] Song LM, Wang G D, Wang H P, Xing N Z, et al. Effect of 2-methoxyestradiol combined with quercetin on prostate cancer in vitro. Zhonghua yi xue za zhi 2016;96(2):95–9.
[205] Wang P, Henning S M, Heber D, Vadgama J V, et al. Sensitization to docetaxel in prostate cancer cells by green tea and quercetin. J Nutr Biochem 2015;26(4):408–15.
[206] Rauf A, Imran M, Khan I A, ur-Rehman M, Gilani S A, Mehmood Z, et al. Anticancer potential of quercetin: a comprehensive review. Phytother Res 2018;32(11):2109–30.
[207] Kalinova J, Dadakova E. Rutin and total quercetin content in amaranth (Amaranthus spp.). Plant Foods Hum Nutr 2009;64(1):68.
[208] Patel K, Patel DK. The beneficial role of rutin, a naturally occurring flavonoid in health promotion and disease prevention: a systematic review and update. Bioact Food Diet Interv Arthritis Relat Inflamm Dis 2019:457–79. doi:10.1016/b978-0-12-813820-5.00026-x.
[209] Arima H, Ashida H, Danno G-i. Rutin-enhanced antibacterial activities of flavonoids against Bacillus cereus and Salmonella enteritidis. BiosciBiotechnolBiochem 2002;66(5):1009–14.
[210] Dixit S. Anticancer effect of rutin isolated from the methanolic extract of Triticum aestivum straw in mice. Med Sci 2014;2(4):153–60.
[211] Gullón B, Lú-Chau T A, Moreira M T, Lema J M, Eibes G, et al. Rutin: a review on extraction, identification and purification methods, biological activities and approaches to enhance its bioavailability. Trends Food Sci Technol 2017;67:220–35.
[212] Jarial R, Shard A, Thakur S, Sakinah M, Zularisam A W, Rezania S, et al. Characterization of flavonoids from fern Cheilanthes tenuifolia and evaluation of antioxidant, antimicrobial and anticancer activities. J King Saud Univ Sci 2018;30(4):425–32.
[213] Itagaki S, Oikawa S, Ogura J, Kobayashi M, Hirano T, Iseki K, et al. Protective effects of quercetin-3-rhamnoglucoside (rutin) on ischemia-reperfusion injury in rat small intestine. Food Chem 2010;118(2):426–9.
[214] Satari A, Amini S A, Raeisi E, Lemoigne Y, Heidarian E, et al. Synergetic impact of combined 5-fluorouracil and rutin on apoptosis in PC3 cancer cells through the modulation of P53 gene expression. Adv Pharm Bull 2019;9(3):462.
[215] Selloum L, Reichl S, Müller M, Sebihi L, Arnhold J, et al. Effects of flavonols on the generation of superoxide anion radicals by xanthine oxidase and stimulated neutrophils. Arch Biochem Biophys 2001;395(1):49–56.
[216] ben Sghaier M, Pagano A, Mousslim M, Ammari Y, Kovacic H, Luis J, et al. Rutin inhibits proliferation, attenuates superoxide production and decreases adhesion and migration of human cancerous cells. Biomed Pharmacother 2016;84:1972–8.
[217] Saleh A, ElFayoumi H M, Youns M, Barakat W, et al. Rutin and orlistat produce antitumor effects via antioxidant and apoptotic actions. Naunyn-Schmiedeberg's Arch Pharmacol 2019;392(2):165–75.
[218] Caparica R, Júlio A, Araújo MEM, Baby A R, Fonte P, Costa J G, et al. Anticancer activity of rutin and its combination with ionic liquids on renal cells. Biomolecules 2020;10(2):233.
[219] Lin JP, Yang J S, Lin J J, Lai K C, Lu H F, Ma C Y, et al. Rutin inhibits human leukemia tumor growth in a murine xenograft model in vivo. Environ Toxicol 2012;27(8):480–4.
[220] Jayameena P, Sivakumari K, Ashok K, Rajesh S, et al. Rutin: a potential anticancer drug against human colon cancer (HCT116) cells. Int. J. Biol. Pharm. Allied Sci 2018;7:1731–45.
[221] Nasri Nasrabadi P, Zareian S, Nayeri Z, Salmanipour R, Parsafar S, Gharib E, et al. A detailed image of rutin underlying intracellular signaling pathways in human SW480 colorectal cancer cells based on miRNAs-lncRNAs-mRNAs-TFs interactions. J Cell Physiol 2019;234(9):15570–80.
[222] Nafees S, Mehdi S H, Zafaryab M, Zeya B, Sarwar T, Rizvi M A, et al. Synergistic interaction of rutin and silibinin on human colon cancer cell line. Arch Med Res 2018;49(4):226–34.
[223] Chang C, Zhang L, Miao Y, Fang B, Yang Z, et al. Anticancer and apoptotic-inducing effects of rutin-chitosan nanoconjugates in triple negative breast cancer cells. J Clust Sci 2020:1–10.
[224] Elsayed HE, Ebrahim H Y, Mohyeldin M M, Siddique A B, Kamal A M, Haggag E G, et al. Rutin as a novel c-met inhibitory lead for the control of triple negative breast malignancies. Nutr Cancer 2017;69(8):1256–71.
[225] Iriti M, Kubina R, Cochis A, Sorrentino R, Varoni E M, Kabała-Dzik A, et al. Rutin, a quercetin glycoside, restores chemosensitivity in human breast cancer cells. Phytother Res 2017;31(10):1529–38.
[226] Chen H, Miao Q, Geng M, Liu J, Hu Y, Tian L, et al. Anti-tumor effect of rutin on human neuroblastoma cell lines through inducing G2/M cell cycle arrest and promoting apoptosis. Sci World J 2013;2013:1–8 Article ID 269165.
[227] Goitia H, Quispe P, Naso L G, Martínez V R, Rey M, Rizzi A C, et al. Interactions of rutin with the oxidovanadium (iv) cation. Anticancer improvement effects of glycosylated flavonoids. New J Chem 2019;43(45):17636–46.
[228] Khan F, Pandey P, Upadhyay T K, Jafri A, Jha N K, Mishra R, et al. Anti-cancerous effect of rutin against HPV-C33A cervical cancer cells via G0/G1 cell cycle arrest and apoptotic induction. Endocr Metab Immune Disord Drug Targets 2020;20(3):409–18.
[229] Ahmad M, Akhtar J, Hussain A, Arshad M, Mishra A, et al. Development of a new rutin nanoemulsion and its application on prostate carcinoma PC3 cell line. EXCLI J 2017;16:810.
[230] Farha AK, Gan RY, Li HB, Wu DT, Atanasov AG, Gul K, et al. The anticancer potential of the dietary polyphenol rutin: current status, challenges, and perspectives. Crit Rev Food Sci Nutr 2020;62(3):1–28.
[231] Imani A, Maleki N, Bohlouli S, Kouhsoltani M, Sharifi S, Maleki Dizaj S, et al. Molecular mechanisms of anticancer effect of rutin. Phytother Res 2020;35(5):2500–13.
[232] Nouri Z, Fakhri S, Nouri K, Wallace C E, Farzaei M H, Bishayee A, et al. Targeting multiple signaling pathways in cancer: the rutin therapeutic approach. Cancers 2020;12(8):2276.
[233] Bonesi M, Loizzo M R, Menichini F, Tundis R, et al.. Flavonoids in treating psoriasis, in Immunity and Inflammation in Health and Disease. Boston: Elsevier; 2018. p. 281–94.
[234] Huang W-H, Lee A-R, Yang C-H. Antioxidative and anti-inflammatory activities of polyhydroxyflavonoids of Scutellaria baicalensis GEORGI. Biosci Biotechnol Biochem 2006;70(10):2371–80.
[235] Ikemoto S, Sugimura K, Yoshida N, Yasumoto R, Wada S, Yamamoto K, et al. Antitumor effects of Scutellariae radix and its components baicalein, baicalin, and wogonin on bladder cancer cell lines. Urology 2000;55(6):951–5.
[236] Li BQ, Fu T, Dongyan Y, Mikovits JA, Ruscetti FW, Wang JM, et al. Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem Biophys Res Commun 2000;276(2):534–8.
[237] Zeng N, Zhang G, Hu X, Pan J, Zhou Z, Gong D, et al. Inhibition mechanism of baicalein and baicalin on xanthine oxidase and their synergistic effect with allopurinol. J Funct Foods 2018;50:172–82.
[238] Li-Weber M. New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein, and Baicalin. Cancer Treat Rev 2009;35(1):57–68.
[239] Wang X-F, Zhou Q M, Du J, Zhang H, Lu Y Y, Su S B, et al. Baicalin suppresses migration, invasion and metastasis of breast cancer via p38MAPK signaling pathway. Anticancer Agents Med Chem 2013;13(6):923–31.
[240] El-Gogary RI, Gaber SAA, Nasr M. Polymeric nanocapsular baicalin: chemometric optimization, physicochemical characterization and mechanistic anticancer approaches on breast cancer cell lines. Sci Rep 2019;9(1):1–14.
[241] Wang N, Tang L J, Zhu G Q, Peng D Y, Wang L, Sun F N, et al. Apoptosis induced by baicalin involving up-regulation of P53 and bax in MCF-7 cells. J Asian Nat Prod Res 2008;10(12):1129–35.
[242] Zhou T, Zhang A, Kuang G, Gong X, Jiang R, Lin D, et al. Baicalin inhibits the metastasis of highly aggressive breast cancer cells by reversing epithelial-to-mesenchymal transition by targeting β-catenin signaling. Oncol Rep 2017;38(6):3599–607.
[243] Zhang X, Tang X, Liu H, Li L, Hou Q, Gao J, et al. Autophagy induced by baicalin involves downregulation of CD147 in SMMC-7721 cells in vitro. Oncol Rep 2012;27(4):1128–34.
[244] Zakki S A, Cui Z G, Sun L, Feng Q W, Li M L, Inadera H, et al. Baicalin augments hyperthermia-induced apoptosis in U937 cells and modulates the MAPK pathway via ROS generation. Cell Physiol Biochem 2018;45(6):2444–60.
[245] Huang Y, Hu J, Zheng J, Li J, Wei T, Zheng Z, et al. Down-regulation of the PI3K/Akt signaling pathway and induction of apoptosis in CA46 Burkitt lymphoma cells by baicalin. J Exp Clin Cancer Res 2012;31(1):1–9.
[246] Lu H-F, Hsueh S C, Ho Y T, Kao M C, Yang J S, Chiu T H, et al. ROS mediates baicalin-induced apoptosis in human promyelocytic leukemia HL-60 cells through the expression of the Gadd153 and mitochondrial-dependent pathway. Anticancer Res 2007;27(1A):117–25.
[247] Ciesielska E, Gwardys A, Metodiewa D. Anticancer, antiradical and antioxidative actions of novel Antoksyd S and its major components, baicalin and baicalein. Anticancer Res 2002;22(5):2885–91.
[248] Orzechowska B, Chaber R, Wiśniewska A, Pajtasz-Piasecka E, Jatczak B, Siemieniec I, et al. Baicalin from the extract of Scutellaria baicalensis affects the innate immunity and apoptosis in leukocytes of children with acute lymphocytic leukemia. Int Immunopharmacol 2014;23(2):558–67.
[249] Yu C, Zhang Z, Zhang H, Zhen Z, Calway T, Wang Y, et al. Pretreatment of baicalin and wogonoside with glycoside hydrolase: A promising approach to enhance anticancer potential. Oncol Rep 2013;30(5):2411–18.
[250] Tao Y, Zhan S, Wang Y, Zhou G, Liang H, Chen X, et al. Baicalin, the major component of traditional Chinese medicine Scutellaria baicalensis induces colon cancer cell apoptosis through inhibition of oncomiRNAs. Sci Rep 2018;8(1):1–11.

[251] Medina J J M, Naso L G, Pérez A L, Rizzi A, Ferrer E G, Williams P A, et al. Antioxidant and anticancer effects and bioavailability studies of the flavonoid baicalin and its oxidovanadium (IV) complex. J Inorg Biochem 2017;166:150–61.
[252] Zhang L, Wang X, Wang R, Zheng X, Li N, Li H, et al. Baicalin potentiates TRAIL–induced apoptosis through p38 MAPK activation and intracellular reactive oxygen species production. Mol Med Rep 2017;16(6):8549–55.
[253] Sui X, Han X, Chen P, Wu Q, Feng J, Duan T, et al. Baicalin induces apoptosis and suppresses the cell cycle progression of lung cancer cells through downregulating Akt/mTOR signaling pathway. Front Mol Biosci 2020;7:323.
[254] Jangid AK, Agraval H, Rai D B, Jain P, Yadav U C, Pooja D, et al. Baicalin encapsulating lipid-surfactant conjugate based nanomicelles: Preparation, characterization and anticancer activity. Chem Phys Lipids 2020;233:104978.
[255] Du G, Han G, Zhang S, Lin H, Wu X, Wang M, et al. Baicalin suppresses lung carcinoma and lung metastasis by SOD mimic and HIF-1α inhibition. Euro J Pharmacol 2010;630(1–3):121–30.
[256] Xu X-F, Cai B L, Guan S M, Li Y, Wu J Z, Wang Y, et al. Baicalin induces human mucoepidermoid carcinoma Mc3 cells apoptosis in vitro and in vivo. Invest New Drugs 2011;29(4):637–45.
[257] Chen J, Li Z, Chen A Y, Ye X, Luo H, Rankin G O, et al. Inhibitory effect of baicalin and baicalein on ovarian cancer cells. Int J Mol Sci 2013;14(3):6012–25.
[258] Zheng Y-C, Shen D D, Ren M, Liu X Q, Wang Z R, Liu Y, et al. Baicalin, a natural LSD1 inhibitor. Bioorg Chem 2016;69:129–31.
[259] Hayami S, Kelly J D, Cho H S, Yoshimatsu M, Unoki M, Tsunoda T, et al. Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers. Int J Cancer 2011;128(3):574–86.
[260] Chan FL, Choi H L, Chen Z Y, Chan P S, Huang Y, et al. Induction of apoptosis in prostate cancer cell lines by a flavonoid, baicalin. Cancer Lett 2000;160(2):219–28.
[261] Peng Y, Guo C, Yang Y, Li F, Zhang Y, Jiang B, et al. Baicalein induces apoptosis of human cervical cancer HeLa cells in vitro. Mol Med Rep 2015;11(3):2129–34.
[262] Zhu Y, Fang J, Wang H, Fei M, Tang T, Liu K, et al. Baicalin suppresses proliferation, migration, and invasion in human glioblastoma cells via Ca2+-dependent pathway. Drug DesDev Ther 2018;12:3247.
[263] Gong W-y, Zhao Z X, Liu B J, Lu L W, Dong J C, et al. Exploring the chemopreventive properties and perspectives of baicalin and its aglycone baicalein in solid tumors. Eur J Med Chem 2017;126:844–52.
[264] Singh S, Meena A, Luqman S. Baicalin mediated regulation of key signaling pathways in cancer. Pharmacol Res 2020:105387.
[265] Chen W-C, Kuo T H, Tzeng Y S, Tsai Y C, et al. Baicalin induces apoptosis in SW620 human colorectal carcinoma cells in vitro and suppresses tumor growth in vivo. Molecules 2012;17(4):3844–57.
[266] Li D, Lin B, Yusuf N, Burns E M, Yu X, Luo D, et al. Proteomic analysis and functional studies of baicalin on proteins associated with skin cancer. Am J Chin Med 2017;45(03):599–614.
[267] Lin C, Tsai S C, Tseng M T, Peng S F, Kuo S C, Lin M W, et al. AKT serine/threonine protein kinase modulates baicalin-triggered autophagy in human bladder cancer T24 cells. Int J Oncol 2013;42(3):993–1000.
[268] Liu Y, Hong Z, Chen P, Wang J, Zhou Y, Huang J, et al. Baicalin inhibits growth and induces apoptosis of human osteosarcoma cells by suppressing the AKT pathway. Oncol Lett 2019;18(3):3188–94.
[269] Ma W, Liu X, Du W. Baicalin induces apoptosis in SW480 cells through down-regulation of the SP1 transcription factor. Anticancer Drugs 2019;30(2):153.
[270] Peng Y, Fu Z Z, Guo C S, Zhang Y X, Di Y, Jiang B, et al. Effects and mechanism of baicalin on apoptosis of cervical cancer HeLa cells in-vitro. Iran J Pharm Res 2015;14(1):251.
[271] Wan D, Ouyang H. Baicalin induces apoptosis in human osteosarcoma cell through ROS-mediated mitochondrial pathway. Nat Prod Res 2018;32(16):1996–2000.
[272] Xu X, Li Q, Yu K, Murtaza G, Liu B, et al. Baicalin-induced cytotoxicity and apoptosis in multidrug-resistant MC3/5FU mucoepidermoid carcinoma cell Line. Lett Drug Des Discov 2019;16(12):1339–47.
[273] Yu Y, Pei M, Li L. Baicalin induces apoptosis in hepatic cancer cells in vitro and suppresses tumor growth in vivo. Int J Clin Exp Med 2015;8(6):8958.
[274] Yu Z, Luo X, Wang C, Ye J, Liu S, Xie L, et al. Baicalin promoted site-2 protease and not site-1 protease in endoplasmic reticulum stress-induced apoptosis of human hepatocellular carcinoma cells. FEBS open bio 2016;6(11):1093–101.
[275] Yang K, Zeng L, Ge A, Chen Z, Bao T, Long Z, et al. Investigating the regulation mechanism of baicalin on triple negative breast cancer's biological network by a systematic biological strategy. Biomed Pharmacother 2019;118:109253.
[276] Li H-B, Chen F. Isolation and purification of baicalein, wogonin and oroxylin A from the medicinal plant Scutellaria baicalensis by high-speed counter-current chromatography. J Chromatogr A 2005;1074(1-2):107–10.
[277] Dinda B, et al. Therapeutic potentials of baicalin and its aglycone, baicalein against inflammatory disorders. Eur J Med Chem 2017;131:68–80.
[278] Kang KA, Zhang R, Piao M J, Chae S, Kim H S, Park J H, et al. Baicalein inhibits oxidative stress-induced cellular damage via antioxidant effects. Toxicol Ind Health 2012;28(5):412–21.
[279] Liu H, Dong Y, Gao Y, Du Z, Wang Y, Cheng P, et al. The fascinating effects of baicalein on cancer: a review. Int J Mol Sci 2016;17(10):1681.
[280] Shao R, Zheng H, Jia S, Jiang Y, Yang Q, Kang G, et al. Nitric oxide enhancing resistance to PEG-induced water deficiency is associated with the primary photosynthesis reaction in Triticum aestivum L. Int J Mol Sci 2018;19(9):2819.
[281] Sowndhararajan K, Deepa P, Kim M, Park S J, Kim S, et al. Baicalein as a potent neuroprotective agent: a review. Biomed Pharmacother 2017;95:1021–32.
[282] Li H-L, Zhang S, Wang Y, Liang R R, Li J, An P, et al. Baicalein induces apoptosis via a mitochondrial-dependent caspase activation pathway in T24 bladder cancer cells. Mol Med Rep 2013;7(1):266–70.
[283] Choi E-O, Park C, Hwang H J, Hong S H, Kim G Y, Cho E J, et al. Baicalein induces apoptosis via ROS-dependent activation of caspases in human bladder cancer 5637 cells. Int J Oncol 2016;49(3):1009–18.
[284] Chao J-I, Su W-C, Liu H-F. Baicalein induces cancer cell death and proliferation retardation by the inhibition of CDC2 kinase and survivin associated with opposite role of p38 mitogen-activated protein kinase and AKT. Mol Cancer Ther 2007;6(11):3039–48.
[285] Han SE, Park C H, Nam-Goong I S, Kim Y I, Kim E S, et al. Anticancer effects of baicalein in FRO thyroid cancer cells through the up-regulation of ERK/p38 MAPK and Akt pathway. in vivo 2019;33(2):375–82.
[286] Han P, Shang J, Chen D L, Li S Y, Fan R Li, R H, Shen D Y, et al. Baicalein mediates anticancer effect on cholangiocarcinoma through co-targeting the AKT/NF-κB and STAT3 signaling pathway. Process Biochem 2021;102:304–14.
[287] Guo J, You H, Li D. Baicalein exerts anticancer effect in nasopharyngeal carcinoma in vitro and in vivo. Oncol Res Featur Preclin Clin Cancer Ther 2019;27(5):601–11.
[288] Pidgeon GP, Kandouz M, Meram A, Honn K V, et al. Mechanisms controlling cell cycle arrest and induction of apoptosis after 12-lipoxygenase inhibition in prostate cancer cells. Cancer Res 2002;62(9):2721–7.
[289] Aryal P, Kim K, Park P H, Ham S, Cho J, Song K, et al. Baicalein induces autophagic cell death through AMPK/ULK1 activation and downregulation of m TORC 1 complex components in human cancer cells. FEBS J 2014;281(20):4644–58.
[290] Yan H, Xin S, Wang H, Ma J, Zhang H, Wei H, et al. Baicalein inhibits MMP-2 expression in human ovarian cancer cells by suppressing the p38 MAPK-dependent NF-κB signaling pathway. Anticancer Drugs 2015;26(6):649–56.
[291] Cathcart M-C, Useckaite Z, Drakeford C, Semik V, Lysaght J, Gately K, et al. Anti-cancer effects of baicalein in non-small cell lung cancer in-vitro and in–vivo. BMC Cancer 2016;16(1):1–13.
[292] Lee H Z, Leung H W C, Lai M Y, Wu C H, et al. Baicalein induced cell cycle arrest and apoptosis in human lung squamous carcinoma CH27 cells. Anticancer Res 2005;25(2A):959–64.
[293] Leung H W, Yang W H, Lai M Y, Lin C J, Lee H Z, et al. Inhibition of 12-lipoxygenase during baicalein-induced human lung nonsmall carcinoma H460 cell apoptosis. Food Chem Toxicol 2007;45(3):403–11.
[294] Takahashi H, Chen M C, Pham H, Angst E, King J C, Park J, et al. Baicalein, a component of Scutellaria baicalensis, induces apoptosis by Mcl-1 down-regulation in human pancreatic cancer cells. Biochimica et Biophysica Acta (BBA)-Mol Cell Res 2011;1813(8):1465–74.
[295] Tian Y, Zhen L, Bai J A, Mei Y, Li Z, Lin A, et al. Anticancer effects of baicalein in pancreatic neuroendocrine tumors in vitro and in vivo. Pancreas 2017;46(8):1076.
[296] Yan W, Ma X, Zhao X, Zhang S, et al. Baicalein induces apoptosis and autophagy of breast cancer cells via inhibiting PI3K/AKT pathway in vivo and vitro. Drug Des Dev Ther 2018;12:3961.
[297] Lee J-H, Li Y C, Ip S W, Hsu S C, Chang N W, Tang N Y, et al. The role of Ca2+ in baicalein-induced apoptosis in human breast MDA-MB-231 cancer cells through mitochondria-and caspase-3-dependent pathway. Anticancer Res 2008;28(3A):1701–11.
[298] Wang Y, Han E, Xing Q, Yan J, Arrington A, Wang C, et al. Baicalein upregulates DDIT4 expression which mediates mTOR inhibition and growth inhibition in cancer cells. Cancer Lett 2015;358(2):170–9.
[299] Ma X, Yan W, Dai Z, Gao X, Ma Y, Xu Q, et al. Baicalein suppresses metastasis of breast cancer cells by inhibiting EMT via downregulation of SATB1 and Wnt/β-catenin pathway. Drug Des Dev Ther 2016;10:1419.
[300] Zhou Q-m, Wang S, Zhang H, Lu Y Y, Wang X F, Motoo Y, et al. The combination of baicalin and baicalein enhances apoptosis via the ERK/p38 MAPK pathway in human breast cancer cells. Acta Pharmacologica Sinica 2009;30(12):1648–58.
[301] Li Q-b, You Y, Chen Z C, Lü J, Shao J, Zou P, et al. Role of baicalein in the regulation of proliferation and apoptosis in human myeloma RPMI8226 cells. Chin Med J 2006;119(11):948–52.
[302] Zheng Y H, Yin L H, Grahn T H M, Ye A F, Zhao Y R, Zhang Q Y, et al. Anticancer effects of baicalein on hepatocellular carcinoma cells. Phytother Res 2014;28(9):1342–8.
[303] Han Z, Zhu S, Han X, Wang Z, Wu S, Zheng R, et al. Baicalein inhibits hepatocellular carcinoma cells through suppressing the expression of CD24. Int Immunopharmacol 2015;29(2):416–22.
[304] Palko-Labuz A, Sroda-Pomianek K, Uryga A, Kostrzewa-Suslow E, Michalak K, et al. Anticancer activity of baicalein and luteolin studied in colorectal adenocarcinoma LoVo cells and in drug-resistant LoVo/Dx cells. Biomed Pharmacother 2017;88:232–41.
[305] Wang C-Z, Zhang C F, Chen L, Anderson S, Lu F, Yuan C S, et al. Colon cancer chemopreventive effects of baicalein, an active enteric microbiome metabolite from baicalin. Int J Oncol 2015;47(5):1749–58.
[306] Liu B, Ding L, Zhang L, Wang S, Wang Y, Wang B, et al. Baicalein induces autophagy and apoptosis through AMPK pathway in human glioma cells. Am J Chin Med 2019;47(06):1405–18.

[307] Wu X, Yang Z, Dang H, Peng H, Dai Z, et al. Baicalein inhibits the proliferation of cervical cancer cells through the GSK3β-dependent pathway. Oncol Res 2018;26(4):645.
[308] Gao Y, Snyder S A, Smith J N, Chen Y C, et al. Anticancer properties of baicalein: a review. Med Chem Res 2016;25(8):1515–23.
[309] Chen H, Gao Y, Wu J, Chen Y, Chen B, Hu J, et al. Exploring therapeutic potentials of baicalin and its aglycone baicalein for hematological malignancies. Cancer Lett 2014;354(1):5–11.
[310] Ke M, Zhang Z, Xu B, Zhao S, Ding Y, Wu X, et al. Baicalein and baicalin promote antitumor immunity by suppressing PD-L1 expression in hepatocellular carcinoma cells. Int Immunopharmacol 2019;75:105824.
[311] Liu J J, Huang T S, Cheng W F, Lu F J, et al. Baicalein and baicalin are potent inhibitors of angiogenesis: inhibition of endothelial cell proliferation, migration and differentiation. Int J Cancer 2003;106(4):559–65.
[312] Wang W, Xi M, Duan X, Wang Y, Kong F, et al. Delivery of baicalein and paclitaxel using self-assembled nanoparticles: synergistic antitumor effect in vitro and in vivo. Int J Nanomed 2015;10:3737.
[313] Park CH, Han S E, Nam-Goong I S, Kim Y I, Kim E S, et al. Combined effects of baicalein and docetaxel on apoptosis in 8505c anaplastic thyroid cancer cells via downregulation of the ERK and Akt/mTOR pathways. Endocrinol Metab 2018;33(1):121.
[314] Chai Y, Xu J, Yan B. The anti-metastatic effect of baicalein on colorectal cancer. Oncol Rep 2017;37(4):2317–23.
[315] Yan X, Rui X, Zhang K. Baicalein inhibits the invasion of gastric cancer cells by suppressing the activity of the p38 signaling pathway. Oncol Rep 2015;33(2):737–43.
[316] Chen Z, Hou R, Gao S, Song D, Feng Y, et al. Baicalein inhibits proliferation activity of human colorectal cancer cells HCT116 through downregulation of ezrin. Cell Physiol Biochem 2018;49(5):2035–46.
[317] Guo Z, Hu X, Xing Z, Xing R, Lv R, Cheng X, et al. Baicalein inhibits prostate cancer cell growth and metastasis via the caveolin-1/AKT/mTOR pathway. Mol Cell Biochem 2015;406(1):111–19.
[318] Kim H J, Park C, Han M H, Hong S H, Kim G Y, Hoon Hong S, et al. Baicalein induces caspase-dependent apoptosis associated with the generation of ROS and the activation of AMPK in human lung carcinoma A549 cells. Drug Dev Res 2016;77(2):73–86.
[319] Ma C, Xu T, Sun X, Zhang S, Liu S, Fan S, et al. Network pharmacology and bioinformatics approach reveals the therapeutic mechanism of action of baicalein in hepatocellular carcinoma. Evid Based Complement Altern Med 2019;2019:1–15 Article ID 7518374.
[320] Mu J, Liu T, Jiang L, Wu X, Cao Y, Li M, et al. The traditional Chinese medicine baicalein potently inhibits gastric cancer cells. J Cancer 2016;7(4):453.
[321] Wu B, Li J, Huang D, Wang W, Chen Y, Liao Y, et al. Baicalein mediates inhibition of migration and invasiveness of skin carcinoma through Ezrin in A431 cells. Bmc Cancer 2011;11(1):1–8.
[322] Zhang Y, Song L, Cai L, Wei R, Hu H, Jin W, et al. Effects of baicalein on apoptosis, cell cycle arrest, migration, and invasion of osteosarcoma cells. Food Chem Toxicol 2013;53:325–33.
[323] Afolayan A, Meyer J. The antimicrobial activity of 3, 5, 7-trihydroxyflavone isolated from the shoots of Helichrysum aureonitens. J Ethnopharmacol 1997;57(3):177–81.
[324] Ciolino H, Yeh G. The flavonoid galangin is an inhibitor of CYP1A1 activity and an agonist/antagonist of the aryl hydrocarbon receptor. Br J Cancer 1999;79(9):1340–6.
[325] Kaur A, Singh R, Dey C S, Sharma S S, Bhutani K K, Singh I P, et al. Antileishmanial phenylpropanoids from Alpinia galanga (Linn.) Willd. Indian J Exp Biol 2010;48:314–17.
[326] Aloud A A, Veeramani C, Govindasamy C, Alsaif M A, Al-Numair K S, et al. Galangin, a natural flavonoid reduces mitochondrial oxidative damage in streptozotocin-induced diabetic rats. Redox Rep 2018;23(1):29–34.
[327] Cushnie T, Lamb A. Assessment of the antibacterial activity of galangin against 4-quinolone resistant strains of Staphylococcus aureus. Phytomedicine 2006;13(3):187–91.
[328] Meyer J J M, Afolayan A J, Taylor M B, Erasmus D, et al. Antiviral activity of galangin isolated from the aerial parts of Helichrysum aureonitens. J Ethnopharmacol 1997;56(2):165–9.
[329] Zhang C, Zhang G, Pan J, Gong D, et al. Galangin competitively inhibits xanthine oxidase by a ping-pong mechanism. Food Res Intl 2016;89:152–60.
[330] Ha TK, Kim M E, Yoon J H, Bae S J, Yeom J, Lee J S, et al. Galangin induces human colon cancer cell death via the mitochondrial dysfunction and caspase-dependent pathway. Exp BiolMed 2013;238(9):1047–54.
[331] Sulaiman GM. Molecular structure and anti-proliferative effect of galangin in HCT-116 cells: in vitro study. Food Sci Biotechnol 2016;25(1):247–52.
[332] Kim DA, Jeon YK, Nam MJ. Galangin induces apoptosis in gastric cancer cells via regulation of ubiquitin carboxy-terminal hydrolase isozyme L1 and glutathione S-transferase P. Food Chem Toxicol 2012;50(3-4):684–8.
[333] Zhang W, Lan Y, Huang Q, Hua Z, et al. Galangin induces B16F10 melanoma cell apoptosis via mitochondrial pathway and sustained activation of p38 MAPK. Cytotechnology 2013;65(3):447–55.
[334] Zhu L, Luo Q, Bi J, Ding J, Ge S, Chen F, et al. Galangin inhibits growth of human head and neck squamous carcinoma cells in vitro and in vivo. Chem Biol Interact 2014;224:149–56.
[335] Zhang H, Li N, Wu J, Su L, Chen X, Lin B, et al. Galangin inhibits proliferation of HepG2 cells by activating AMPK via increasing the AMP/TAN ratio in a LKB1-independent manner. Euro J Pharmacol 2013;718(1–3):235–44.
[336] Li Y, Guo M, Lin Z, Zhao M, Xia Y, Wang C, et al. Multifunctional selenium nanoparticles with Galangin-induced HepG2 cell apoptosis through p38 and AKT signalling pathway. Royal Soc Open Sci 2018;5(11):180509.
[337] Zhong X, Huang S, Liu D, Jiang Z, Jin Q, Li. C.,et al. Galangin promotes cell apoptosis through suppression of H19 expression in hepatocellular carcinoma cells. Cancer Med 2020;9(15):5546–57.
[338] Huang H, Chen A Y, Rojanasakul Y, Ye X, Rankin G O, Chen Y C, et al. Dietary compounds galangin and myricetin suppress ovarian cancer cell angiogenesis. J Funct Foods 2015;15:464–75.
[339] Huang H, Chen A Y, Ye X, Guan R, Rankin G O, Chen Y C, et al. Galangin, a flavonoid from lesser Galangal, induced apoptosis via p53-dependent pathway in ovarian cancer cells. Molecules 2020;25(7):1579.
[340] Al-Shammari A M, Al-Saadi H, Al-Shammari S M, Jabir M S, et al. Galangin enhances gold nanoparticles as anti-tumor agents against ovarian cancer cells. In: AIP Conference Proceedings. AIP Publishing LLC; 2020.
[341] Cao J, Wang H, Chen F, Fang J, Xu A, Xi W, et al. Galangin inhibits cell invasion by suppressing the epithelial-mesenchymal transition and inducing apoptosis in renal cell carcinoma. Mol Med Rep 2016;13(5):4238–44.
[342] Yang Z, Li X, Han W, Lu X, Jin S, Yang W, et al. Galangin suppresses human osteosarcoma cells: an exploration of its underlying mechanism. Oncol Rep 2017;37(1):435–41.
[343] Chen D, Li D, Xu X B, Qiu S, Luo S, Qiu E, et al. Galangin inhibits epithelial-mesenchymal transition and angiogenesis by downregulating CD44 in glioma. J Cancer 2019;10(19):4499.
[344] Kong Y, Feng Z, Chen A, Qi Q, Han M, Wang S, et al. The natural flavonoid galangin elicits apoptosis, pyroptosis, and autophagy in glioblastoma. Front Oncol 2019;9:942.
[345] Xiong Y, Lai X, Xiang W, Zhou J, Han J, Li H, et al. Galangin (GLN) suppresses proliferation, migration, and invasion of human glioblastoma cells by targeting Skp2-induced epithelial–mesenchymal transition (EMT). OncoTargets Ther 2020;13:9235.
[346] Lei D, Zhang F, Yao D, Xiong N, Jiang X, Zhao H, et al. Galangin increases ERK1/2 phosphorylation to decrease ADAM9 expression and prevents invasion in A172 glioma cells. Mol Med Rep 2018;17(1):667–73.
[347] Kumar R, Tiku A. Galangin induces cell death by modulating the expression of glyoxalase-1 and Nrf-2 in HeLa cells. Chem Biol Interact 2018;279:1–9.
[348] Zhu Y, Rao Q, Zhang X, Zhou X, et al. Galangin induced antitumor effects in human kidney tumor cells mediated via mitochondrial mediated apoptosis, inhibition of cell migration and invasion and targeting PI3K/AKT/mTOR signalling pathway. J. BUON 2018;23:795–9.
[349] Wang H-X, Tang C. Galangin suppresses human laryngeal carcinoma via modulation of caspase-3 and AKT signaling pathways. Oncol Rep 2017;38(2):703–14.
[350] Zou Y, Li R, Kuang D, Zuo M, Li W, Tong W, et al. Galangin inhibits cholangiocarcinoma cell growth and metastasis through downregulation of microrna-21 expression. BioMed Res Int 2020;2020:1–13 Article ID 5846938.
[351] Lee C-C, Lin M L, Meng M, Chen S S, et al. Galangin induces p53-independent S-phase arrest and apoptosis in human nasopharyngeal carcinoma cells through inhibiting PI3K–AKT signaling pathway. Anticancer Res 2018;38(3):1377–89.
[352] Chung K W, Jeong H O, Lee E K, Kim S J, Chun P, Chung H Y, et al. Evaluation of antimelanogenic activity and mechanism of galangin in silico and in vivo. Biol Pharm Bull 2018;41(1):73–9.
[353] Wang L, Xue J, Wei F, Zheng G, Cheng M, Liu S, et al. Chemopreventive effect of galangin against benzo (a) pyrene-induced stomach tumorigenesis through modulating aryl hydrocarbon receptor in Swiss albino mice. Hum Exp Toxicol 2021;40(9):1434–44.
[354] Song W, Yan C Y, Zhou Q Q, Zhen L L, et al. Galangin potentiates human breast cancer to apoptosis induced by TRAIL through activating AMPK. Biomed Pharmacother 2017;89:845–56.
[355] Fang D, Xiong Z, Xu J, Yin J, Luo R, et al. Chemopreventive mechanisms of galangin against hepatocellular carcinoma: a review. Biomed Pharmacother 2019;109:2054–61.
[356] Ren K, Zhang W, Wu G, Ren J, Lu H, Li Z, et al. Synergistic anti-cancer effects of galangin and berberine through apoptosis induction and proliferation inhibition in oesophageal carcinoma cells. Biomed Pharmacother 2016;84:1748–59.
[357] Choi YJ, Lee YH, Lee S-T. Galangin and kaempferol suppress phorbol-12-myristate-13-acetate-induced matrix metalloproteinase-9 expression in human fibrosarcoma HT-1080 cells. Mol Cells 2015;38(2):151.
[358] Pandey Y, Khan M A, Mehdi S H, Sati S C, Bhatt P, Pant C K, et al. Synergistic effect of galangin and TNF inhibits the cell proliferation and induces cell apoptosis through activating caspases pathways in breast cancer. J Pharmacogn Phytochem 2019;8(2):2024–30.
[359] Zhang W, Huang Q, Hua Z. Galangin and TRAIL cooperate to suppress A549 lung cancer proliferation via apoptosis and p38 MAPK activation. Acta Pharmaceutica Sinica B 2012;2(6):569–74.
[360] Yao H, Lu H, Zhang J, Xue X, Yin C, Hu J, et al. Preparation of prolonged–circulating Galangin-loaded liposomes and evaluation of antitumor efficacy in vitro and pharmacokinetics in vivo. J Nanomater 2019;2019:1–9 Article ID 7236895.
[361] Sabry S, Okda T, Hasan A. Formulation, characterization, and evaluation of the anti-tumor activity of nanosized galangin loaded niosomes on chemically induced hepatocellular carcinoma in rats. J Drug Deliv Sc Technol 2021;61:102163.

[362] Basli A, Soulet S, Chaher N, Mérillon J M, Chibane M, Monti J P, et al. Wine polyphenols: potential agents in neuroprotection. Oxid Med Cell Longev 2012;2012:1–14 Article ID 805762.
[363] Holland T M, Agarwal P, Wang Y, Leurgans S E, Bennett D A, Booth S L, et al. Dietary flavonols and risk of Alzheimer dementia. Neurology 2020;94(16):e1749–56.
[364] Ozcan C, Yaman M. Determination of myricetin in medicinal plants by high--performance liquid chromatography. Instrum Sci Technol 2015;43(1):44–52.
[365] Xu X, Wang H J, Murphy P A, Cook L, Hendrich S, et al. Daidzein is a more bioavailable soymilk isoflavone than is genistein in adult women. J Nutr 1994;124(6):825–32.
[366] Zang W, Wang T, Wang Y, Li M, Xuan X, Ma Y, et al. Myricetin exerts anti-proliferative, anti-invasive, and pro-apoptotic effects on esophageal carcinoma EC9706 and KYSE30 cells via RSK2. Tumor Biol 2014;35(12):12583–92.
[367] Nagao A, Seki M, Kobayashi H. Inhibition of xanthine oxidase by flavonoids. Biosci Biotechnol Biochem 1999;63(10):1787–90.
[368] Li Y, Frenz C M, Li Z, Chen M, Wang Y, Li F, et al. Virtual and In vitro bioassay screening of phytochemical inhibitors from flavonoids and isoflavones against xanthine oxidase and cyclooxygenase-2 for gout treatment. ChemBiol Drug Des 2013;81(4):537–44.
[369] Kang HR, Moon J Y, Ediriweera M K, Song Y W, Cho M, Kasiviswanathan D, et al. Dietary flavonoid myricetin inhibits invasion and migration of radioresistant lung cancer cells (A549-IR) by suppressing MMP-2 and MMP-9 expressions through inhibition of the FAK-ERK signaling pathway. Food Sci Nutr 2020;8(4):2059–67.
[370] Kim M E, Ha T K, Yoon J H, Lee J S, et al. Myricetin induces cell death of human colon cancer cells via BAX/BCL2-dependent pathway. Anticancer Res 2014;34(2):701–6.
[371] Ye C, Zhang C, Huang H, Yang B, Xiao G, Kong D, et al. The natural compound myricetin effectively represses the malignant progression of prostate cancer by inhibiting PIM1 and disrupting the PIM1/CXCR4 interaction. Cell Physiol Biochem 2018;48(3):1230–44.
[372] Ma L, Cao X, Wang H, Lu K, Wang Y, Tu C, et al. Discovery of myricetin as a potent inhibitor of human flap endonuclease 1, which potentially can be used as sensitizing agent against HT-29 human colon cancer cells. J Agric Food Chem 2019;67(6):1656–65.
[373] Chiu W -T, Shen S C, Chow J M, Lin C W, Shia L T, Chen Y C, et al. Contribution of reactive oxygen species to migration/invasion of human glioblastoma cells U87 via ERK-dependent COX-2/PGE2 activation. Neurobiol Dis 2010;37(1):118–29.
[374] Tang X -J, Huang K M, Gui H, Wang J J, Lu J T, Dai L J, et al. Pluronic-based micelle encapsulation potentiates myricetin-induced cytotoxicity in human glioblastoma cells. Int J Nanomed 2016;11:4991.
[375] Li H -G, Chen J X, Xiong J H, Zhu J W, et al. Myricetin exhibits anti-glioma potential by inducing mitochondrial-mediated apoptosis, cell cycle arrest, inhibition of cell migration and ROS generation. J BUON 2016;21(1):182–190.
[376] Wang G, Wang J J, Tang X J, Du L, Li F, et al. In vitro and in vivo evaluation of functionalized chitosan–pluronic micelles loaded with myricetin on glioblastoma cancer. NanomedNanotechnol Biol Med 2016;12(5):1263–78.
[377] Shih Y -W, Wu P F, Lee Y C, Shi M D, Chiang T A, et al. Myricetin suppresses invasion and migration of human lung adenocarcinoma A549 cells: possible mediation by blocking the ERK signaling pathway. J Agric Food Chem 2009;57(9):3490–9.
[378] Rajendran P, Maheshwari U, Muthukrishnan A, Muthuswamy R, Anand K, Ravindran B, et al. Myricetin: versatile plant based flavonoid for cancer treatment by inducing cell cycle arrest and ROS–reliant mitochondria-facilitated apoptosis in A549 lung cancer cells and in silico prediction. Mol Cell Biochem 2021;476(1):57–68.
[379] Ci Y, Zhang Y, Liu Y, Lu S, Cao J, Li H, et al. Myricetin suppresses breast cancer metastasis through down-regulating the activity of matrix metalloproteinase (MMP)-2/9. Phytother Res 2018;32(7):1373–81.
[380] Lin Y, Cai L. Environmental and dietary factors and lung cancer risk among Chinese women: a case-control study in southeast China. Nutr Cancer 2012;64(4):508–14.
[381] Sun F, Zheng X Y, Ye J, Wu T T, Wang J L, Chen W, et al. Potential anticancer activity of myricetin in human T24 bladder cancer cells both in vitro and in vivo. Nutr Cancer 2012;64(4):599–606.
[382] Zhou Z, Mao W, Li Y, Qi C, He Y, et al. Myricetin inhibits breast tumor growth and angiogenesis by regulating VEGF/VEGFR2 and p38MAPK signaling pathways. Anat Rec 2019;302(12):2186–92.
[383] Mohan U P, Sriram B, Panneerselvam T, Devaraj S, MubarakAli D, Parasuraman P, et al. Utilization of plant-derived Myricetin molecule coupled with ultrasound for the synthesis of gold nanoparticles against breast cancer. Naunyn-Schmiedeberg's Arch Pharmacol 2020;393:1963–76.
[384] Jung S K, Lee K W, Byun S, Kang N J, Lim S H, Heo Y S, et al. Myricetin suppresses UVB-induced skin cancer by targeting Fyn. Cancer Res 2008;68(14):6021–9.
[385] Jung S K, Lee K W, Byun S, Lee E J, Kim J E, Bode A M, et al. Myricetin inhibits UVB-induced angiogenesis by regulating PI-3 kinase in vivo. Carcinogenesis 2010;31(5):911–17.
[386] Kim GD. Myricetin inhibits angiogenesis by inducing apoptosis and suppressing PI3K/Akt/mTOR signaling in endothelial cells. J Cancer Prev 2017;22(4):219.
[387] Kang N J, Jung S K, Lee K W, Lee H J, et al. Myricetin is a potent chemopreventive phytochemical in skin carcinogenesis. Ann NY Acad Sci 2011;1229(1):124–32.
[388] Sun W, Tao Y, Yu D, Zhao T, Wu L, Yu W, et al. Myricetin exerts potent anticancer effects on human skin tumor cells. Trop J Pharm Res 2018;17(6):1067–72.
[389] Akhtar S, Najafzadeh M, Isreb M, Newton L, Gopalan R C, Anderson D, et al. Anticancer potential of myricetin bulk and nano forms in vitro in lymphocytes from myeloma patients. Arch Toxicol 2021;95(1):337–43.
[390] Yi J -L, Shi S, Shen Y L, Wang L, Chen H Y, Zhu J, et al. Myricetin and methyl eugenol combination enhances the anticancer activity, cell cycle arrest and apoptosis induction of cis-platin against HeLa cervical cancer cell lines. Int J Clin Exp Pathol 2015;8(2):1116.
[391] Mondal S, Jana J, Sengupta P, Jana S, Chatterjee S, et al. Myricetin arrests human telomeric G-quadruplex structure: a new mechanistic approach as an anticancer agent. Mol BioSyst 2016;12(8):2506–18.
[392] Jiao D, Zhang XD. Myricetin suppresses p21-activated kinase 1 in human breast cancer MCF-7 cells through downstream signaling of the β-catenin pathway. Oncol Rep 2016;36(1):342–8.
[393] Knickle A, Fernando W, Greenshields A L, Rupasinghe H V, Hoskin D W, et al. Myricetin-induced apoptosis of triple-negative breast cancer cells is mediated by the iron-dependent generation of reactive oxygen species from hydrogen peroxide. Food Chem Toxicol 2018;118:154–67.
[394] Maroufi N F, Vahedian V, Mazrakhondi S A M, Kooti W, Khiavy H A, Bazzaz R, et al. Sensitization of MDA-MBA231 breast cancer cell to docetaxel by myricetin loaded into biocompatible lipid nanoparticles via sub-G1 cell cycle arrest mechanism. Naunyn-Schmiedeberg's Arch Pharmacol 2020;393(1):1–11.
[395] Huang H, Chen A Y, Ye X, Li B, Rojanasakul Y, Rankin G O, et al. Myricetin inhibits proliferation of cisplatin-resistant cancer cells through a p53-dependent apoptotic pathway. Int J Oncol 2015;47(4):1494–502.
[396] Xu Y, Xie Q, Wu S, Yi D, Yu Y, Liu S, et al. Myricetin induces apoptosis via endoplasmic reticulum stress and DNA double-strand breaks in human ovarian cancer cells. Mol Med Rep 2016;13(3):2094–100.
[397] Ha T K, Jung I, Kim M E, Bae S K, Lee J S, et al. Anti-cancer activity of myricetin against human papillary thyroid cancer cells involves mitochondrial dysfunction–mediated apoptosis. Biomed Pharmacother 2017;91:378–84.
[398] Jo S, Ha T K, Han S H, Kim M E, Jung I, Lee H W, et al. Myricetin induces apoptosis of human anaplastic thyroid cancer cells via mitochondria dysfunction. Anticancer Res 2017;37(4):1705–10.
[399] Iyer SC, Gopal A, Halagowder D. Myricetin induces apoptosis by inhibiting P21 activated kinase 1 (PAK1) signaling cascade in hepatocellular carcinoma. Mol Cell Biochem 2015;407(1):223–37.
[400] Zhang X-H, Chen S Y, Tang L, Shen Y Z, Luo L, Xu C, et al. Myricetin induces apoptosis in HepG2 cells through Akt/p70S6K/bad signaling and mitochondrial apoptotic pathway. Anticancer Agents Med Chem 2013;13(10):1575–81.
[401] Seydi E, Rasekh H R, Salimi A, Mohsenifar Z, Pourahmad J, et al. Myricetin selectively induces apoptosis on cancerous hepatocytes by directly targeting their mitochondria. Basic Clin Pharmacol Toxicol 2016;119(3):249–58.
[402] Li M, Chen J, Yu X, Xu S, Li D, Zheng Q, et al. Myricetin suppresses the propagation of hepatocellular carcinoma via down-regulating expression of YAP. Cells 2019;8(4):358.
[403] Pan H, Hu Q, Wang J, Liu Z, Wu D, Lu W, et al. Myricetin is a novel inhibitor of human inosine 5′-monophosphate dehydrogenase with anti-leukemia activity. Biochem Biophys Res Commun 2016;477(4):915–22.
[404] Feng J, Chen X, Wang Y, Du Y, Sun Q, Zang W, et al. Myricetin inhibits proliferation and induces apoptosis and cell cycle arrest in gastric cancer cells. Mol Cell Biochem 2015;408(1):163–70.
[405] Devi K P, Rajavel T, Habtemariam S, Nabavi S F, Nabavi S M, et al. Molecular mechanisms underlying anticancer effects of myricetin. Life Sci 2015;142:19–25.
[406] Jiang M, Zhu M, Wang L, Yu S, et al. Anti-tumor effects and associated molecular mechanisms of myricetin. Biomed Pharmacother 2019;120:109506.
[407] Xie Y, Wang Y, Xiang W, Wang Q, Cao Y, et al. Molecular mechanisms of the action of Myricetin in cancer. Mini Rev Med Chem 2020;20(2):123–33.
[408] Afroze N, Pramodh S, Hussain A, Waleed M, Vakharia K, et al. A review on myricetin as a potential therapeutic candidate for cancer prevention. 3 Biotech 2020;10(5):1–12.
[409] Maggioni D, Nicolini G, Rigolio R, Biffi L, Pignataro L, Gaini R, et al. Myricetin and naringenin inhibit human squamous cell carcinoma proliferation and migration in vitro. Nutr Cancer 2014;66(7):1257–67.
[410] Varela-Rodríguez L, Sánchez-Ramírez B, Hernández-Ramírez V I, Varela-Rodríguez H, Castellanos-Mijangos R D, González-Horta C, et al. Effect of gallic acid and myricetin on ovarian cancer models: a possible alternative antitumoral treatment. BMC Complement Med Ther 2020;20:1–16.
[411] Zhang S, Wang L, Liu H, Zhao G, Ming L, et al. Enhancement of recombinant myricetin on the radiosensitivity of lung cancer A549 and H1299 cells. Diagn Pathol 2014;9(1):1–7.
[412] Hussain J, Ali L, Khan A L, Ur Rehman N, Jabeen F, Kim J S, et al. Isolation and bioactivities of the flavonoids morin and morin-3-O-β-D-glucopyranoside from Acridocarpus orientalis—a wild Arabian medicinal plant. Molecules 2014;19(11):17763–72.
[413] Lamounier K C, Cunha L C S, De Morais S A L, De Aquino F J T, Chang R, Do Nascimento E A, et al. Chemical analysis and study of phenolics, antioxidant activity, and antibacterial effect of the wood and bark of maclura tinctoria

(L.) D. Don ex Steud. Evid Based Complement Alternat Med 2012;2012:1–7 Article ID 451039.
[414] Osman A, Makris D. Oxidation of morin (2′, 3, 4′, 5, 7-Pentahydroxylavone) with a peroxidase homogenate from onion. Int Food Res J, 2011;18(3):1085–9.
[415] Rattanachaikunsopon P, Phumkhachorn P. Bacteriostatic effect of flavonoids isolated from leaves of Psidium guajava on fish pathogens. Fitoterapia 2007;78(6):434–6.
[416] Tsao R, Yang R, Young JC. Antioxidant isoflavones in osage orange, Maclura pomifera (Raf.) Schneid. J Agric Food Chem 2003;51(22):6445–51.
[417] Ji Y, Jia L, Zhang Y, Xing Y, Wu X, Zhao B, et al. Antitumor activity of the plant extract morin in tongue squamous cell carcinoma cells. Oncol Rep 2018;40(5):3024–32.
[418] Ola M S, Aleisa A M, Al-Rejaie S S, Abuohashish H M, Parmar M Y, Alhomida A S, et al. Flavonoid, morin inhibits oxidative stress, inflammation and enhances neurotrophic support in the brain of streptozotocin-induced diabetic rats. Neurol Sci 2014;35(7):1003–8.
[419] Cos P, Ying L, Calomme M, Hu J P, Cimanga K, Van Poel B, et al. Structure–activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. J Nat Prod 1998;61(1):71–6.
[420] Choudhury A, Chakraborty I, Banerjee T S, Vana D R, Adapa D, et al. Efficacy of morin as a potential therapeutic phytocomponent: insights into the mechanism of action. Int J Med Res Health Sci 2017;6(11):175–94.
[421] Iio M, Moriyama A, Matsumoto Y, Takaki N, Fukumoto M, et al. Inhibition of xanthine oxidase by flavonoids. Agric Biol Chem 1985;49(7):2173–6.
[422] Wang C P, Wang X, Zhang X, Shi Y W, Liu L, Kong L D, et al. Morin improves urate excretion and kidney function through regulation of renal organic ion transporters in hyperuricemic mice. J Pharm & Pharm Sci 2010;13(3):411–27.
[423] Gupta SC, Phromnoi K, Aggarwal BB. Morin inhibits STAT3 tyrosine 705 phosphorylation in tumor cells through activation of protein tyrosine phosphatase SHP1. Biochem Pharmacol 2013;85(7):898–912.
[424] Yao D, Cui H, Zhou S, Guo L, et al. Morin inhibited lung cancer cells viability, growth, and migration by suppressing miR-135b and inducing its target CCNG2. Tumor Biol 2017;39(10):1010428317712443.
[425] Hyun H B, Lee W S, Go S I, Nagappan A, Park C, Han M H, et al. The flavonoid morin from Moraceae induces apoptosis by modulation of Bcl-2 family members and Fas receptor in HCT 116 cells. Int J Oncol 2015;46(6):2670–8.
[426] Chung S S, Oliva B, Dwabe S, Vadgama J V, et al. Combination treatment with flavonoid morin and telomerase inhibitor MST–312 reduces cancer stem cell traits by targeting STAT3 and telomerase. Int J Oncol 2016;49(2):487–98.
[427] Sithara T, Arun K B, Syama H P, Reshmitha T R, Nisha P, et al. Morin inhibits proliferation of SW480 colorectal cancer cells by inducing apoptosis mediated by reactive oxygen species formation and uncoupling of warburg effect. Front Pharmacol 2017;8:640.
[428] Chen R, Zhang L. Morin inhibits colorectal tumor growth through inhibition of NF-κB signaling pathway. Immunopharmacol Immunotoxicol 2019;41(6):622–9.
[429] Sharma S H, Thulasingam S, Chellappan D R, Chinnaswamy P, Nagarajan S, et al. Morin and Esculetin supplementation modulates c-myc induced energy metabolism and attenuates neoplastic changes in rats challenged with the procarcinogen 1, 2-dimethylhydrazine. Euro J Pharmacol 2017;796:20–31.
[430] Kuo H M, Chang L S, Lin Y L, Lu H F, Yang J S, Lee J H, et al. Morin inhibits the growth of human leukemia HL-60 cells via cell cycle arrest and induction of apoptosis through mitochondria dependent pathway. Anticancer Res 2007;27(1A):395–405.
[431] Karimi R, Parivar K, Roudbari N H, Sadeghi S V, Hashemi M, Hayat P, et al. Anti-proliferative and apoptotic effects of morin in human Leukemia cell lines (HUT-78). Int. J. Cell. Mol. Biotechnol 2013;2013:1–13.
[432] Park C, Lee W S, Go S I, Nagappan A, Han M H, Hong S H, et al. Morin, a flavonoid from moraceae, induces apoptosis by induction of BAD protein in human leukemic cells. Int J Mol Sci 2015;16(1):645–59.
[433] Nie ZY, Yang L, Liu X J, Yang Z, Yang G S, Zhou J, et al. Morin inhibits proliferation and induces apoptosis by modulating the miR-188-5p/PTEN/AKT regulatory pathway in CML cells. Mol Cancer Ther 2019;18(12):2296–307.
[434] Pereira WL, de Oliveira T T, Kanashiro M M, Filardi M A, da Costa M R, da Costa L M, et al. Morin exhibits leukemic cellular apoptosis through caspase pathway. Nat Prod Res 2020;35(23):5554–8.
[435] Bieg D, Sypniewski D, Nowak E, Bednarek I, et al. Morin decreases galectin-3 expression and sensitizes ovarian cancer cells to cisplatin. Arch Gynecol Obstet 2018;298(6):1181–94.
[436] Nowak E, Sypniewski D, Bednarek I. Morin exerts anti-metastatic, anti-proliferative and anti-adhesive effect in ovarian cancer cells: an in vitro studies. Mol Biol Rep 2020;47(3):1965–78.
[437] Naso LG, Lezama L, Rojo T, Etcheverry S B, Valcarcel M, Roura M, et al. Biological evaluation of morin and its new oxovanadium (IV) complex as antio-xidant and specific anti-cancer agents. Chem Biol Interact 2013;206(2):289–301.
[438] Jin H, Lee W S, Eun S Y, Jung J H, Park H S, Kim G, et al. Morin, a flavonoid from Moraceae, suppresses growth and invasion of the highly metastatic breast cancer cell line MDA-MB–231 partly through suppression of the Akt pathway. Int J Oncol 2014;45(4):1629–37.
[439] Lee J, Jin H, Lee W S, Nagappan A, Choi Y H, Kim G S, et al. Morin, a flavonoid from moraceae, inhibits cancer cell adhesion to endothelial cells and EMT by downregulating VCAM1 and ncadherin. Asian Pac J Cancer Prev 2016;17(7):3071–5.
[440] Sivaramakrishnan V, Shilpa P N M, Kumar V R P, Devaraj S N, et al. Attenuation of N-nitrosodiethylamine-induced hepatocellular carcinogenesis by a novel flavonol—Morin. Chem Biol Interact 2008;171(1):79–88.
[441] Sivaramakrishnan V, Devaraj SN. Morin fosters apoptosis in experimental hepatocellular carcinogenesis model. Chem Biol Interact 2010;183(2):284–92.
[442] Hwang-Bo H, Lee W S, Nagappan A, Kim H J, Panchanathan R, Park C, et al. Morin enhances auranofin anticancer activity by up-regulation of DR4 and DR5 and modulation of Bcl-2 through reactive oxygen species generation in Hep3B human hepatocellular carcinoma cells. Phytother Res 2019;33(5):1384–93.
[443] Zhang Q, Zhang F, Thakur K, Wang J, Wang H, Hu F, et al. Molecular mechanism of anti-cancerous potential of morin extracted from mulberry in Hela cells. Food Chem Toxicol 2018;112:466–75.
[444] Ding X, Yin C, Zhang W, Sun Y, Zhang Z, Yang E, et al. Designing aptamer–gold nanoparticle-loaded pH-sensitive liposomes encapsulate morin for treating cancer. Nanoscale Res Lett 2020;15:1–17.
[445] Solairaja S, Andrabi M Q, Dunna N R, Venkatabalasubramanian S, et al. Overview of morin and its complementary role as an adjuvant for anticancer agents. Nutr Cancer 2020;73(6):927–42.
[446] Hostetler GL, Ralston RA, Schwartz SJ. Flavones: Food sources, bioavailability, metabolism, and bioactivity. Adv Nutr 2017;8(3):423–35.
[447] Zhao R, Chen Z, Jia G, Li J, Cai Y, Shao X, et al. Protective effects of diosmetin extracted from Galium verum L. on the thymus of U14-bearing mice. Can J Physiol Pharmacol 2011;89(9):665–73.
[448] Androutsopoulos VP, Mahale S, Arroo R R, Potter G, et al. Anticancer effects of the flavonoid diosmetin on cell cycle progression and proliferation of MDA-MB 468 breast cancer cells due to CYP1 activation. Oncol Rep 2009;21(6):1525–8.
[449] Koosha S, Mohamed Z, Sinniah A, Alshawsh M A, et al. Evaluation of anti–tumorigenic effects of diosmetin against human colon cancer xenografts in athymic nude mice. Molecules 2019;24(14):2522.
[450] Morel I, Lescoat G, Cogrel P, Sergent O, Pasdeloup N, Brissot P, et al. Antioxidant and iron-chelating activities of the flavonoids catechin, quercetin and diosmetin on iron-loaded rat hepatocyte cultures. Biochem Pharmacol 1993;45(1):13–19.
[451] Androutsopoulos V, Wilsher N, Arroo R R, Potter G A, et al. Bioactivation of the phytoestrogen diosmetin by CYP1 cytochromes P450. Cancer Lett 2009;274(1):54–60.
[452] Wang C, Li S, Ren H, Sheng Y, Wang T, Li M, et al. Anti-proliferation and pro-apoptotic effects of diosmetin via modulating cell cycle arrest and mitochondria-mediated intrinsic apoptotic pathway in MDA-MB-231 cells. Med Sci Monit 2019;25:4639.
[453] Androutsopoulos VP, Spandidos DA. The flavonoids diosmetin and luteolin exert synergistic cytostatic effects in human hepatoma HepG2 cells via CYP1A-catalyzed metabolism, activation of JNK and ERK and P53/P21 up-regulation. J Nutr Biochem 2013;24(2):496–504.
[454] Liu B, Shi Y, Peng W, Zhang Q, Liu J, Chen N, et al. Diosmetin induces apoptosis by upregulating p53 via the TGF-β signal pathway in HepG2 hepatoma cells. Mol Med Rep 2016;14(1):159–64.
[455] Liu J, Ren H, Liu B, Zhang Q, Li M, Zhu R, et al. Diosmetin inhibits cell proliferation and induces apoptosis by regulating autophagy via the mammalian target of rapamycin pathway in hepatocellular carcinoma HepG2 cells. Oncol Lett 2016;12(6):4385–92.
[456] Liu J, Wen X, Liu B, Zhang Q, Zhang J, Miao H, et al. Diosmetin inhibits the metastasis of hepatocellular carcinoma cells by downregulating the expression levels of MMP–2 and MMP–9. Mol Med Rep 2016;13(3):2401–8.
[457] Qiao J, Liu J, Jia K, Li N, Liu B, Zhang Q, et al. Diosmetin triggers cell apoptosis by activation of the p53/Bcl-2 pathway and inactivation of the Notch3/NF-κB pathway in HepG2 cells. Oncol Lett 2016;12(6):5122–8.
[458] Ma A, Zhang R. Diosmetin inhibits cell proliferation, induces cell apoptosis and cell cycle arrest in liver cancer. Cancer Manag Res 2020;12:3537.
[459] Oak C, Khalifa A O, Isali I, Bhaskaran N, Walker E, Shukla S, et al. Diosmetin suppresses human prostate cancer cell proliferation through the induction of apoptosis and cell cycle arrest. Int J Oncol 2018;53(2):835–43.
[460] Choi J, Lee D H, Park S Y, Seol J W, et al. Diosmetin inhibits tumor development and block tumor angiogenesis in skin cancer. Biomed Pharmacother 2019;117:109091.
[461] Chen X, Wu Q, Chen Y, Zhang J, Li H, Yang Z, et al. Diosmetin induces apoptosis and enhances the chemotherapeutic efficacy of paclitaxel in non-small cell lung cancer cells via Nrf2 inhibition. Br J Pharmacol 2019;176(12):2079–94.
[462] Koosha S, Mohamed Z, Sinniah A, Alshawsh M A, et al. Investigation into the molecular mechanisms underlying the anti-proliferative and anti-tumorigenesis activities of diosmetin against HCT-116 human colorectal cancer. Sci Rep 2019;9(1):1–17.
[463] Qiu M, Liu J, Su Y, Guo R, Zhao B, Liu J, et al. Diosmetin induces apoptosis by downregulating AKT phosphorylation via P53 activation in human renal carcinoma ACHN cells. Protein Pept Lett 2020;27(10):1022–8.
[464] Roma A, Rota SG, Spagnuolo PA. Diosmetin induces apoptosis of acute myeloid leukemia cells. Mol Pharm 2018;15(3):1353–60.
[465] Chan EWC, Ng Y K, Tan C Y, Alessandro L, Wong S K, Chan H T, et al. Diosmetin and tamarixetin (methylated flavonoids): a review on their chemistry, sources, pharmacology, and anticancer properties. J Appl PharmSci 2021;11(03):022–8.
[466] Asensi M, Ortega A, Mena S, Feddi F, Estrela J M, et al. Natural polyphenols in cancer therapy. Crit Rev Clin Lab Sci 2011;48(5–6):197–216.

[467] Zu Y, Li C, Fu Y, Zhao C, et al. Simultaneous determination of catechin, rutin, quercetin kaempferol and isorhamnetin in the extract of sea buckthorn (Hippophae rhamnoides L.) leaves by RP-HPLC with DAD. J Pharm Biomed Anal 2006;41(3):714–19.
[468] Hu S, Huang L, Meng L, Sun H, Zhang W, Xu Y, et al. Isorhamnetin inhibits cell proliferation and induces apoptosis in breast cancer via Akt and mitogen–activated protein kinase kinase signaling pathways. Mol Med Rep 2015;12(5):6745–51.
[469] Yang JH, Kim S C, Shin B Y, Jin S H, Jo M J, Jegal K H, et al. O-methylated flavonol isorhamnetin prevents acute inflammation through blocking of NF-κB activation. Food Chem Toxicol 2013;59:362–72.
[470] Zuo A, Yanying Y, Li J, Binbin X, Xiongying Y, Yan Q, et al. Study on the relation of structure and antioxidant activity of isorhamnetin, quercetin, phloretin, silybin and phloretin isonicotinyl hydrazone. Free Radic Antioxid 2011;1(4):39–47.
[471] Kim J E, Lee D E, Lee K W, Son J E, Seo S K, Li J, et al. Isorhamnetin suppresses skin cancer through direct inhibition of MEK1 and PI3-K. Cancer Prev Res 2011;4(4):582–91.
[472] Ramachandran L, Manu K A, Shanmugam M K, Li F, Siveen K S, Vali S, et al. Isorhamnetin inhibits proliferation and invasion and induces apoptosis through the modulation of peroxisome proliferator-activated receptor γ activation pathway in gastric cancer. J Biol Chem 2012;287(45):38028–40.
[473] Li C, Yang X, Chen C, Cai S, Hu J, et al. Isorhamnetin suppresses colon cancer cell growth through the PI3K–Akt–mTOR pathway. Mol Med Rep 2014;9(3):935–40.
[474] Saud SM, Young M R, Jones-Hall Y L, Ileva L, Evbuomwan M O, Wise J, et al. Chemopreventive activity of plant flavonoid isorhamnetin in colorectal cancer is mediated by oncogenic Src and β-catenin. Cancer Res 2013;73(17):5473–84.
[475] Antunes-Ricardo M, Moreno-García B E, Gutiérrez-Uribe J A, Aráiz-Hernández D, Alvarez M M, Serna-Saldivar S O, et al. Induction of apoptosis in colon cancer cells treated with isorhamnetin glycosides from Opuntia ficus-indica pads. Plant Foods Hum Nutr 2014;69(4):331–6.
[476] Luan Y, Luan Y, Zhao Y, Xiong F, Li Y, Liu L, et al. Isorhamnetin in Tsoong blocks Hsp70 expression to promote apoptosis of colon cancer cells. Saudi J Biol Sci 2019;26(5):1011–22.
[477] Antunes-Ricardo M, Hernández-Reyes A, Uscanga-Palomeque A C, Rodríguez–Padilla C, Martínez-Torres A C, Gutiérrez-Uribe J A, et al. Isorhamnetin glycoside isolated from Opuntia ficus-indica (L.) MiII induces apoptosis in human colon cancer cells through mitochondrial damage. Chem Biol Interact 2019;310:108734.
[478] Manu KA, Shanmugam M K, Ramachandran L, Li F, Siveen K S, Chinnathambi A, et al. Isorhamnetin augments the anti-tumor effect of capecitabine through the negative regulation of NF-κB signaling cascade in gastric cancer. Cancer Lett 2015;363(1):28–36.
[479] Li C, Yang D, Zhao Y, Qiu Y, Cao X, Yu Y, et al. Inhibitory effects of isorhamnetin on the invasion of human breast carcinoma cells by downregulating the expression and activity of matrix metalloproteinase-2/9. Nutr Cancer 2015;67(7):1191–200.
[480] Wu Q, Kroon P A, Shao H, Needs P W, Yang X, et al. Differential effects of quercetin and two of its derivatives, isorhamnetin and isorhamnetin-3-glucuronide, in inhibiting the proliferation of human breast-cancer MCF-7 cells. J Agric Food Chem 2018;66(27):7181–9.
[481] Hu J, Zhang Y, Jiang X, Zhang H, Gao Z, Li Y, et al. ROS-mediated activation and mitochondrial translocation of CaMKII contributes to Drp1-dependent mitochondrial fission and apoptosis in triple-negative breast cancer cells by isorhamnetin and chloroquine. J Exp Clin Cancer Res 2019;38(1):1–16.
[482] Duan R, Liang X, Chai B, Zhou Y, Du H, Suo Y, et al. Isorhamnetin induces melanoma cell apoptosis via the PI3K/Akt and NF-κB pathways. BioMed Res Int 2020;2020:1–11 Article ID 1057943.
[483] Wang J L, Quan Q, Ji R, Guo X Y, Zhang J M, Li X, et al. Isorhamnetin suppresses PANC-1 pancreatic cancer cell proliferation through S phase arrest. Biomed Pharmacother 2018;108:925–33.
[484] Zhang B Y, Wang Y M, Gong H, Zhao H, Lv X Y, Yuan G H, et al. Isorhamnetin flavonoid synergistically enhances the anticancer activity and apoptosis induction by cis-platin and carboplatin in non-small cell lung carcinoma (NSCLC). Int J Clin Exp Pathol 2015;8(1):25.
[485] Li Q, Ren F Q, Yang C L, Zhou L M, Liu Y Y, Xiao J, et al. Anti-proliferation effects of isorhamnetin on lung cancer cells in vitro and in vivo. Asian Pac J Cancer Prev 2015;16(7):3035–42.
[486] Ruan Y, Hu K, Chen H. Autophagy inhibition enhances isorhamnetin–induced mitochondria–dependent apoptosis in non–small cell lung cancer cells. Mol Med Rep 2015;12(4):5796–806.
[487] Luo W, Liu Q, Jiang N, Li M, Shi L, et al. Isorhamnetin inhibited migration and invasion via suppression of Akt/ERK-mediated epithelial-to-mesenchymal transition (EMT) in A549 human non-small-cell lung cancer cells. Biosci Rep 2019;39(9):1–13 BSR20190159.
[488] Du Y, Jia C, Liu Y, Li Y, Wang J, Sun K, et al. Isorhamnetin enhances the radiosensitivity of A549 cells through interleukin-13 and the NF-k B signaling pathway. Front Pharmacol 2020;11:2324.
[489] Chen Q, Song S, Wang Z, Shen Y, Xie L, Li J, et al. Isorhamnetin induces the paraptotic cell death through ROS and the ERK/MAPK pathway in OSCC cells. Oral Dis 2021;27(2):240–50.
[490] Park C, Cha H J, Choi E O, Lee H, Hwang-Bo H, Ji S Y, et al. Isorhamnetin induces cell cycle arrest and apoptosis via reactive oxygen species-mediated AMP-activated protein kinase signaling pathway activation in human bladder cancer cells. Cancers 2019;11(10):1494.
[491] Cai F, Zhang Y, Li J, Huang S, Gao R, et al. Isorhamnetin inhibited the proliferation and metastasis of androgen-independent prostate cancer cells by targeting the mitochondrion-dependent intrinsic apoptotic and PI3K/Akt/mTOR pathway. Biosci Rep 2020;40(3):1–14 BSR20192826.
[492] Wei J, Su H, Bi Y, Li J, Feng L, Sheng W, et al. Anti-proliferative effect of isorhamnetin on HeLa cells through inducing G2/M cell cycle arrest. Exp Ther Med 2018;15(4):3917–23.
[493] Yang B, Zhang F, Yuan W, Du L, Jiang X, et al. Preparation of isorhamnetin nanoparticles and their targeting efficiency to nasopharynx cancer. J Nanosci Nanotechnol 2021;21(2):1293–9.
[494] Yang J, Sun Z. Effect of different isorhamnetin of different density cultured rat c6 glioma cells in vitro. In: Proceedings of Anticancer Research, 2; 2018.
[495] Zou Y, Lu Y, Wei D. Antioxidant activity of a flavonoid-rich extract of Hypericum perforatum L. in vitro. J Agric Food Chem 2004;52(16):5032–9.
[496] Kim S J, Um J Y, Hong S H, Lee J Y, et al. Anti-inflammatory activity of hyperoside through the suppression of nuclear factor-κB activation in mouse peritoneal macrophages. Am J Chin Med 2011;39(01):171–81.
[497] Liu Z, Tao X, Zhang C, Lu Y, Wei D, et al. Protective effects of hyperoside (quercetin-3-o-galactoside) to PC12 cells against cytotoxicity induced by hydrogen peroxide and tert-butyl hydroperoxide. Biomed Pharmacother 2005;59(9):481–90.
[498] Verma N, Amresh G, Sahu P K, Mishra N, Rao C V, Singh A P, et al. Pharmacological evaluation of hyperin for antihyperglycemic activity and effect on lipid profile in diabetic rats. Indian J Exp Biol 2013;51(1):65–72.
[499] Kong Y, Sun W, Wu P. Hyperoside exerts potent anticancer activity in skin cancer. Front Biosci (Landmark edition) 2020;25:463–79.
[500] Li Y, Wang Y, Li L, Kong R, Pan S, Ji L, et al. Hyperoside induces apoptosis and inhibits growth in pancreatic cancer via Bcl-2 family and NF-κB signaling pathway both in vitro and in vivo. Tumor Biol 2016;37(6):7345–55.
[501] Li W, Liu M, Xu Y F, Feng Y, Che J P, Wang G C, et al. Combination of quercetin and hyperoside has anticancer effects on renal cancer cells through inhibition of oncogenic microRNA-27a. Oncol Rep 2014;31(1):117–24.
[502] Qiu J, Zhang T, Zhu X, Yang C, Wang Y, Zhou N, et al. Hyperoside induces breast cancer cells apoptosis via ROS-mediated NF-κB signaling pathway. Int J Mol Sci 2020;21(1):131.
[503] Yang Y, Tantai J, Sun Y, Zhong C, Li Z, et al. Effect of hyperoside on the apoptosis of A549 human non–small cell lung cancer cells and the underlying mechanism. Mol Med Rep 2017;16(5):6483–8.
[504] Yang F Q, Liu M, Li W, Che J P, Wang G C, Zheng J H, et al. Combination of quercetin and hyperoside inhibits prostate cancer cell growth and metastasis via regulation of microRNA–21. Mol Med Rep 2015;11(2):1085–92.
[505] Mertens-Talcott SU, Talcott ST, Percival SS. Low concentrations of quercetin and ellagic acid synergistically influence proliferation, cytotoxicity and apoptosis in MOLT-4 human leukemia cells. J Nutr 2003;133(8):2669–74.
[506] Zhang F, Zhu F B, Li J J, Zhang P P, Zhu J F, et al. Hyperoside enhances the suppressive effects of arsenic trioxide on acute myeloid leukemia cells. Int J Clin Exp Med 2015;8(9):15290.
[507] Boukes GJ, van de Venter M. The apoptotic and autophagic properties of two natural occurring prodrugs, hyperoside and hypoxoside, against pancreatic cancer cell lines. Biomed Pharmacother 2016;83:617–26.
[508] Lü P. Inhibitory effects of hyperoside on lung cancer by inducing apoptosis and suppressing inflammatory response via caspase-3 and NF-κB signaling pathway. Biomed Pharmacother 2016;82:216–25.
[509] Liu Y H, Liu G H, Mei J J, Wang J, et al. The preventive effects of hyperoside on lung cancer in vitro by inducing apoptosis and inhibiting proliferation through Caspase-3 and P53 signaling pathway. Biomed Pharmacother 2016;83:381–91.
[510] Hu Z, Zhao P, Xu H. Hyperoside exhibits anticancer activity in non–small cell lung cancer cells with T790M mutations by upregulating FoxO1 via CCAT1. Oncol Rep 2020;43(2):617–24.
[511] Fu T, Wang L, Jin X N, Sui H J, Liu Z, Jin Y, et al. Hyperoside induces both autophagy and apoptosis in non-small cell lung cancer cells in vitro. Acta Pharmacologica Sinica 2016;37(4):505–18.
[512] Li J P, Liao X H, Xiang Y, Yao A, Song R H, Zhang Z J, et al. Hyperoside and let-7a-5p synergistically inhibits lung cancer cell proliferation via inducing G1/S phase arrest. Gene 2018;679:232–40.
[513] Chen D, Wu Y X, Qiu Y B, Wan B B, Liu G, Chen J L, et al. Hyperoside suppresses hypoxia-induced A549 survival and proliferation through ferrous accumulation via AMPK/HO-1 axis. Phytomedicine 2020;67:153138.
[514] Li F R, Yu F X, Yao S T, Si Y H, Zhang W, Gao L L, et al. Hyperin extracted from manchurian rhododendron leaf induces apoptosis in human endometrial cancer cells through a mitochondrial pathway. Asian Pac J Cancer Prev 2012;13(8):3653–6.
[515] Ping M-H. Hyperin controls the development and therapy of gastric cancer via regulating Wnt/β-Catenin signaling. Cancer Manag Res 2020;12:11773.
[516] Zhang N, Ying M D, Wu Y P, Zhou Z H, Ye Z M, Li H, et al. Hyperoside, a flavonoid compound, inhibits proliferation and stimulates osteogenic differentiation of human osteosarcoma cells. PloS one 2014;9(7):e98973.
[517] Zhu X, Ji M, Han Y, Guo Y, Zhu W, Gao F, et al. PGRMC1-dependent autophagy by hyperoside induces apoptosis and sensitizes ovarian cancer cells to cisplatin treatment. Int J Oncol 2017;50(3):835–46.
[518] Zhang Y, Dong H, Zhang J, Zhang L, et al. Inhibitory effect of hyperoside isolated from Zanthoxylum bungeanum leaves on SW620 human colorectal can-

cer cells via induction of the p53 signaling pathway and apoptosis. Mol Med Rep 2017;16(2):1125–32.
[519] Guon TE, Chung HS. Hyperoside and rutin of Nelumbo nucifera induce mitochondrial apoptosis through a caspase-dependent mechanism in HT-29 human colon cancer cells. Oncol Lett 2016;11(4):2463–70.
[520] Guo W, Yu H, Zhang L, Chen X, Liu Y, Wang Y, et al. Effect of hyperoside on cervical cancer cells and transcriptome analysis of differentially expressed genes. Cancer Cell Int 2019;19(1):1–14.
[521] Alves R C, Almeida I M, Casal S, Oliveira M B P, et al. Isoflavones in coffee: influence of species, roast degree, and brewing method. J Agric Food Chem 2010;58(5):3002–7.
[522] Coward L, Barnes N C, Setchell K D, Barnes S, et al. Genistein, daidzein, and their. beta.-glycoside conjugates: antitumor isoflavones in soybean foods from American and Asian diets. J Agric Food Chem 1993;41(11):1961–7.
[523] Fedoreyev S A, Pokushalova T V, Veselova M V, Glebko L I, Kulesh N I, Muzarok T I, et al. Isoflavonoid production by callus cultures of Maackia amurensis. Fitoterapia 2000;71(4):365–72.
[524] Wang H, Li Q, Chen H. Genistein affects histone modifications on Dickkopf-related protein 1 (DKK1) gene in SW480 human colon cancer cell line. PloS one 2012;7(7):e40955.
[525] Hong H, Landauer M R, Foriska M A, Ledney G D, et al. Antibacterial activity of the soy isoflavone genistein. J Basic Microbiol 2006;46(4):329–35.
[526] Park C E, Yun H, Lee E B, Min B I, Bae H, Choe W, et al. The antioxidant effects of genistein are associated with AMP-activated protein kinase activation and PTEN induction in prostate cancer cells. J Med Food 2010;13(4):815–20.
[527] Sauter D, Schwarz S, Wang K, Zhang R, Sun B, Schwarz W, et al. Genistein as antiviral drug against HIV ion channel. Planta Medica 2014;80(08/09):682–7.
[528] Su S J, Yeh T M, Chuang W J, Ho C L, Chang K L, Cheng H L, et al. The novel targets for anti-angiogenesis of genistein on human cancer cells. Biochem Pharmacol 2005;69(2):307–18.
[529] Verdrengh M, Jonsson I M, Holmdahl R, Tarkowski A, et al. Genistein as an anti-inflammatory agent. Inflamm Res 2003;52(8):341–6.
[530] Akimoto T, Nonaka T, Ishikawa H, Sakurai H, Saitoh J I, Takahashi T, et al. Genistein, a tyrosine kinase inhibitor, enhanced radiosensitivity in human esophageal cancer cell lines in vitro: possible involvement of inhibition of survival signal transduction pathways. Int J Radiat Oncol BiolPhys 2001;50(1):195–201.
[531] Davis J N, Singh B, Bhuiyan M, Sarkar F H, et al. Genistein-induced upregulation of p21 WAF1, downregulation of cyclin B, and induction of apoptosis in prostate cancer cells. Nutr. Cancer 1998;32(3):123–31.
[532] Gong L, Li Y, Nedeljkovic-Kurepa A, Sarkar F H, et al. Inactivation of NF-κB by genistein is mediated via Akt signaling pathway in breast cancer cells. Oncogene 2003;22(30):4702–9.
[533] Russo M, Russo G L, Daglia M, Kasi P D, Ravi S, Nabavi S F, et al. Understanding genistein in cancer: The “good” and the “bad” effects: a review. Food Chem 2016;196:589–600.
[534] Yu Z, Li W, Liu F. Inhibition of proliferation and induction of apoptosis by genistein in colon cancer HT-29 cells. Cancer Lett 2004;215(2):159–66.
[535] Lian F, Bhuiyan M, Li Y W, Wall N, Kraut M, Sarkar F H, et al. Genistein-induced G2-M arrest, p21WAF1 upregulation, and apoptosis in a non-small-cell lung cancer cell line. Nutr Cancer 1998;31(3):184–91.
[536] Gadgeel S M, Ali S, Philip P A, Wozniak A, Sarkar F H, et al. Retracted: Genistein enhances the effect of epidermal growth factor receptor tyrosine kinase inhibitors and inhibits nuclear factor kappa B in nonsmall cell lung cancer cell lines. Cancer 2009;115(10):2165–76.
[537] Zhang J, Su H, Li Q, Li J, Zhao Q, et al. Genistein decreases A549 cell viability via inhibition of the PI3K/AKT/HIF-1α/VEGF and NF-κB/COX-2 signaling pathways. Mol Med Rep 2017;15(4):2296–302.
[538] Fu Z, Cao X, Liu L, Cao X, Cui Y, Li X, et al. Genistein inhibits lung cancer cell stem–like characteristics by modulating MnSOD and FoxM1 expression. Oncol Lett 2020;20(3):2506–15.
[539] Lian F, Li Y, Bhuiyan M, Sarkar F H, et al. p53-independent apoptosis induced by genistein in lung cancer cells. Nutr Cancer 1999;33(2):125–31.
[540] Tian T, Li J, Li B, Wang Y, Li M, Ma D, et al. Genistein exhibits anti-cancer effects via down-regulating FoxM1 in H446 small-cell lung cancer cells. Tumor Biol 2014;35(5):4137–45.
[541] Yang Y, Zang A, Jia Y, Shang Y, Zhang Z, Ge K, et al. Genistein inhibits A549 human lung cancer cell proliferation via miR-27a and MET signaling. Oncol Lett 2016;12(3):2189–93.
[542] Yu Y, Xing Y, Zhang Q, Zhang Q, Huang S, Li X, et al. Soy isoflavone genistein inhibits hsa_circ_0031250/miR-873-5p/FOXM1 axis to suppress non-small-cell lung cancer progression. IUBMB life 2021;73(1):92–107.
[543] Choi EJ, Kim T, Lee M-S. Pro-apoptotic effect and cytotoxicity of genistein and genistin in human ovarian cancer SK-OV-3 cells. Life Sci 2007;80(15):1403–8.
[544] Matsukawa Y, Marui N, Sakai T, Satomi Y, Yoshida M, Matsumoto K, et al. Genistein arrests cell cycle progression at G2-M. Cancer Res 1993;53(6):1328–31.
[545] Xiao X, Liu Z, Wang R, Wang J, Zhang S, Cai X, et al. Genistein suppresses FLT4 and inhibits human colorectal cancer metastasis. Oncotarget 2015;6(5):3225.
[546] Khaw A K, Yong J W Y, Kalthur G, Hande M P, et al. Genistein induces growth arrest and suppresses telomerase activity in brain tumor cells. Genes Chromosom Cancer 2012;51(10):961–74.
[547] Dai W, Wang F, He L, Lin C, Wu S, Chen P, et al. Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial–mesenchymal transition: partial mediation by the transcription factor NFAT1. Mol Carcinog 2015;54(4):301–11.
[548] Hörmann V, Kumi-Diaka J, Durity M, Rathinavelu A, et al. Anticancer activities of genistein-topotecan combination in prostate cancer cells. J Cell Mol Med 2012;16(11):2631–6.
[549] Pintova S, Dharmupari S, Moshier E, Zubizarreta N, Ang C, Holcombe R F, et al. Genistein combined with FOLFOX or FOLFOX–Bevacizumab for the treatment of metastatic colorectal cancer: Phase I/II pilot study. Cancer Chemother Pharmacol 2019;84(3):591–8.
[550] Cheng J, Qi J, Li X T, Zhou K, Xu J H, Zhou Y, et al. ATRA and genistein synergistically inhibit the metastatic potential of human lung adenocarcinoma cells. Int J Clin Exp Med 2015;8(3):4220.
[551] Wu T C, Lin Y C, Chen H L, Huang P R, Liu S Y, Yeh S L, et al. The enhancing effect of genistein on apoptosis induced by trichostatin A in lung cancer cells with wild type p53 genes is associated with upregulation of histone acetyltransferase. Toxicol Appl Pharmacol 2016;292:94–102.
[552] Chen L, Cao H, Huang Q, Xiao J, Teng H, et al. Absorption, metabolism, and bioavailability of flavonoids: a review. Crit Rev Food Sci Nutr 2021;2021:1–13. doi:10.1080/10408398.2021.1917508.
[553] Aiello P, Consalvi S, Poce G, Raguzzini A, Toti E, Palmery M, et al. Dietary flavonoids: nano delivery and nanoparticles for cancer therapy. in Seminars in cancer biology. Elsevier 2021;69:150–65. doi:10.1016/j.semcancer.2019.08.029.
[554] Enaru B, Socaci S, Farcas A, Socaciu C, Danciu C, Stanila A, et al. Novel delivery systems of polyphenols and their potential health benefits. Pharmaceuticals 2021;14(10):946.
[555] Lakshmi B A, Reddy A S, Sangubotla R, Hong J W, Kim S, et al. Ruthenium (II)-curcumin liposome nanoparticles: Synthesis, characterization, and their effects against cervical cancer. Coll Surf B: Biointerface 2021;204:111773.
[556] Galati G, O'brien PJ. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. Free Radic Biol Med 2004;37(3):287–303.
[557] Vogiatzoglou A, Mulligan A A, Lentjes M A, Luben R N, Spencer J P, Schroeter H, et al. Flavonoid intake in European adults (18 to 64 years). PloS one 2015;10(5):e0128132.
[558] Lamartiniere CA, Zhang J-X, Cotroneo MS. Genistein studies in rats: potential for breast cancer prevention and reproductive and developmental toxicity. Am J Clin Nutr 1998;68(6) 1400S–1405S.
[559] Zhang Y, Li Q, Zhou D, Chen H, et al. Genistein, a soya isoflavone, prevents azoxymethane-induced up-regulation of WNT/β-catenin signalling and reduces colon pre-neoplasia in rats. Br J Nutr 2013;109(1):33–42.
[560] Spagnuolo C, Russo G L, Orhan I E, Habtemariam S, Daglia M, Sureda A, et al. Genistein and cancer: current status, challenges, and future directions. Adv Nutr 2015;6(4):408–19.
[561] Li J, Zhang J, Wang Y, Liang X, Wusiman Z, Yin Y, et al. Synergistic inhibition of migration and invasion of breast cancer cells by dual docetaxel/quercetin-loaded nanoparticles via Akt/MMP-9 pathway. Int J Pharm 2017;523(1):300–9.
[562] Zou H, Ye H, Kamaraj R, Zhang T, Zhang J, Pavek P, et al. A review on pharmacological activities and synergistic effect of quercetin with small molecule agents. Phytomedicine 2021;92:153736.
[563] Mandal A K, Ghosh D, Sarkar S, Ghosh A, Swarnakar S, Das N, et al. Nanocapsulated quercetin downregulates rat hepatic MMP-13 and controls diethylnitrosamine-induced carcinoma. Nanomedicine 2014;9(15):2323–2337.
[564] Solairaja S, Andrabi M Q, Dunna N R, Venkatabalasubramanian S, et al. Overview of morin and its complementary role as an adjuvant for anticancer agents. Nutr Cancer 2021;73(6):927–42.
[565] Bhattacharya S, Mondal L, Mukherjee B, Dutta L, Ehsan I, Debnath M C, et al. Apigenin loaded nanoparticle delayed development of hepatocellular carcinoma in rats. Nanomed Nanotechnol Biol Med 2018;14(6):1905–17.
[566] Chen W T L, Yang T S, Chen H C, Chen H H, Chiang H C, Lin T C, et al. Effectiveness of a novel herbal agent MB-6 as a potential adjunct to 5-fluoracil–based chemotherapy in colorectal cancer. Nutr Res 2014;34(7):585–94.
[567] Khan H, Ullah H, Martorell M, Valdes S E, Belwal T, Tejada S, et al. Flavonoids nanoparticles in cancer: Treatment, prevention and clinical prospects. in Seminars in cancer biology. Elsevier 2021;69:200–11. doi:10.1016/j.semcancer.2019.07.023.
[568] Wang X, Yang Y, An Y, Fang G, et al. The mechanism of anticancer action and potential clinical use of kaempferol in the treatment of breast cancer. Biomed Pharmacother 2019;117:109086.
[569] Hussain SA, Sullivan R. Cancer control in Bangladesh. Jpn J Clin Oncol 2013;43(12):1159–69.
[570] Chen C Y, Liu T Z, Liu Y W, Tseng W C, Liu R H, Lu F J, et al. 6-Shogaol (alkanone from ginger) induces apoptotic cell death of human hepatoma p53 mutant Mahlavu subline via an oxidative stress-mediated caspase-dependent mechanism. J Agric Food Chem 2007;55(3):948–54.
[571] Fauziya S, Krishnamurthy R. Papaya (Carica papaya): source material for anticancer. CIBTech J Pharm Sci 2013;2(1):25–34.
[572] Keawsa-ard S, Liawruangrath B, Kongtaweelert S. Bioactive compounds from mesua ferrea stems. Chiang Mai J Sci 2015;42(1):185–95.
[573] Limtrakul P, Pitchakarn P, Suzuki S, Kuguacin J. A triterpenoid from momordica charantia linn: a comprehensive review of anticarcinogenic properties. Carcinogenesis. London: InTech; 2013.

[574] Huq AK, Jamal JA, Stanslas J. Ethnobotanical, phytochemical, pharmacological, and toxicological aspects of persicaria hydropiper (L.) Delarbre. Evid Based Complement Alternat Med 2014;2014:782830.
[575] Anwar F, Latif S, Ashraf M, Gilani A H, et al. Moringa oleifera: a food plant with multiple medicinal uses. Phytother Res 2007;21(1):17–25.
[576] Haibru V. Ocimum sanctum: a potential source of anti-cancer agent and its role in restoration of Maspin via Snail and HDACs in Breast cancer. Diss National Institute of Technology Rourkela; 2014.
[577] Hasan S A, Uddin M M, Huda K N U, Das A, Tabassum N, Hossain M R, et al. Ethnomedicinal plants of two village folk medicinal practitioners in Rajshahi district, Bangladesh: comparison of their folk medicinal uses with Ayurvedic uses. Am-Eur J Sustain Agr 2014;8:10–19.
[578] Matławska I, Sikorska M. Flavonoid compounds in the flowers of Abutilon indicum (L.) Sweet (Malvaceae). Acta poloniae pharmaceutica 2002;59(3):227–9.
[579] Ferdoushi A, Mahmud S, Rana M M, Islam M S, Salauddin A B A, Hossain M F, et al. A survey on medicinal plant usage by folk medicinal practitioners in different villages at Nalitabari Upazilla, Sherpur District, Bangladesh. Eur J Med Plants 2016;11(3):1–22.
[580] Kahramanoğlu İ, Chen C, Chen J, Wan C, et al. Chemical constituents, antimicrobial activity, and food preservative characteristics of Aloe vera gel. Agronomy 2019;9(12):831.
[581] Rao Y K, Fang S H, Hsieh S C, Yeh T H, Tzeng Y M, et al. The constituents of Anisomeles indica and their anti-inflammatory activities. J Ethnopharmacol 2009;121(2):292–6.
[582] Roy S, Uddin M Z, Hassan M A, Rahman M M, et al. Medico-botanical report on the Chakma community of Bangladesh. Bangladesh J Plant Taxon 2008;15(1):67–72.
[583] Yusuf M, Wahab M A, Yousuf M D, Chowdhury J U, Begum J, et al. Some tribal medicinal plants of Chittagong hill tracts, Bangladesh. Bangladesh J Plant Taxon 2007;14(2):117–28.
[584] Kitdamrongtham W, Ishii K, Ebina K, Zhang J, Ukiya M, Koike K, et al. Limonoids and flavonoids from the flowers of Azadirachta indica var. siamensis, and their melanogenesis-inhibitory and cytotoxic activities. Chem Biodivers 2014;11(1):73–84.
[585] Li J, Li H, Kadota S, Namba T, Miyahara T, Khan U G, et al. Effects on cultured neonatal mouse calvaria of the flavonoids isolated from Boerhaavia repens. J Nat Prod 1996;59(11):1015–18.
[586] Ibrahim A K, Radwan M M, Ahmed S A, Slade D, Ross S A, ElSohly M A, et al. Microbial metabolism of cannflavin A and B isolated from Cannabis sativa. Phytochemistry 2010;71(8–9):1014–19.
[587] Mawla F, Khatoon S, Rehana F, Jahan S, Shelley M M R, Hossain S, et al. Ethnomedicinal plants of folk medicinal practitioners in four villages of Natore and Rajshahi districts, Bangladesh. Am Eur J Sustain Agric 2012;6:406–16.
[588] Rahman A, Debnath A. Ethno-botanical study at the village Pondit Para under Palash Upazila of Narsingdi District, Bangladesh. Int J Adv Res 2015;3(5):1037–52.
[589] Zhao W, Zeng X, Zhang T, Wang L, Yang G, Chen Y K, et al. Flavonoids from the bark and stems of Cassia fistula and their anti-tobacco mosaic virus activities. Phytochemistry Lett 2013;6(2):179–82.
[590] Mohamed Z S, Hayssam M A, et al. Antimicrobial activities and phytochemical composition of extracts of Ficus species: an over view. Afr J Microbiol Res 2013;7(33):4207–19.
[591] Walid R, Suvro K F A, Harun-or-Rashid M, Mukti M, Rahman S, Rahmatullah M, et al. Ethnomedicinal plants of folk medicinal practitioners of two villages in Bagerhat district of Bangladesh. Am-Eur J Sustain Agr 2013;7:61–74.
[592] Rahman A M, Kabir E Z M F, Islam A R, Zaman A T M N, et al. Medico-botanical investigation by the tribal people of Naogaon district, Bangladesh. J Med Plants 2013;1(4):136–47.
[593] Dandekar SP, Bajpai ND, Sakharwade SN. A multifunctional Hemidesmus indicus as cosmetic agent: a review article. Int J of Sci Dev & Res 2018;3(10).
[594] Rezwan Walid KFAS, Harun-or-Rashid Md, Mukti Mohsina, Rahman Shahnaz, Rahmatullah Mohammed. Ethnomedicinal plants of folk medicinal practitioners of two villages in Bagerhat district of Bangladesh. Am-Eur J Sustain Agric 2013;7(2):74.
[595] Prajogo B E, Guliet D, Queiroz F E, Wolfender J L, Cholies N Z, Aucky H, et al. Isolation of male antifertility compound in n-butanol fraction of Justicia gendarussa Burm. F. leaves. Folia Medica Indonesiana 2009;45(1):28.
[596] Staubmann R, Schubert-Zsilavecz M, Hiermann A, Kartnig T, et al. A complex of 5-hydroxypyrrolidin-2-one and pyrimidine-2, 4-dione isolated from Jatropha curcas. Phytochemistry 1999;50(2):337–8.
[597] Brishty S R, Islam Setu N, Anwar M, Jahan R, Mia M M K, Fahim Kadir M, et al. Ethnobotanical study on medicinal plants for dermatological disorders at Chittagong Hill Tracts, Bangladesh. Pharm Biomed Res 2020;6(1):61–90.
[598] Okunade AL. Ageratum conyzoides L. (Asteraceae). Fitoterapia 2002;73(1):16.
[599] Rahman A, Islam J, Jahan S, Hossain M S, Rehana F, Haq W M, et al. Differences in selection of medicinal plants between folk and tribal medicine: a case study of a Santal tribal and a non-Santal folk medicinal practitioner in two adjoining districts of Bangladesh. Am-Eur J Sustain Agric 2013;7(2):85–98.
[600] Uddin S.N. Traditional uses of ethnomedicinal plants of the Chittagong Hill Tracts. 1st ed. Dhaka: Bangladesh Nat Herbarium, Bangladesh; 2006.
[601] Islam MT, Tahara S. Dihydroflavonols from Lannea coromandelica. Phytochemistry 2000;54(8):901–7.
[602] Jia S, Shen M, Zhang F, Xie J, et al. Recent advances in Momordica charantia: functional components and biological activities. Int J Mol Sci 2017;18(12):2555.
[603] Rahmatullah M, Ferdausi D, Mollik A, Jahan R, Chowdhury M H, Haque W M, et al. A survey of medicinal plants used by Kavirajes of Chalna area, Khulna district, Bangladesh. Afr J Tradit Complement Altern Med 2010;7(2):91–7.
[604] Shervington L A, Li B S, Shervington A A, Alpan N, Patel R, Muttakin U, et al. A comparative HPLC analysis of myricetin, quercetin and kaempferol flavonoids isolated from gambian and indian moringa oleifera leaves. Int J Chem 2018;10(4):28–37.
[605] Grayer R J, Kite G C, Veitch N C, Eckert M R, Marin P D, Senanayake P, et al. Leaf flavonoid glycosides as chemosystematic characters in Ocimum. Biochem Syst Ecol 2002;30(4):327–42.
[606] Joy A C, Das P, Islam Z, Priya R J, Neaz M, Pervez M, et al. Ethnomedicinal plants of Rakhain tribal communities of two areas of Patuakhali district. J Chem Pharm Res 2014;6(11):550–5.
[607] Rahmatullah M, Jahan F I, Seraj S, Khatun Z, Islam F, Sattar M M, et al. Correlation between non-conventional plants consumed during food scarcity and their folk medicinal usages: a case study in two villages of Kurigram district, Bangladesh. Am-Eur J Sustain Agric 2011;5(2):240–6.
[608] Rahmatullah M, Noman A, Hossan M S, Rashid M H, Rahman T, Chowdhury M H, et al. A survey of medicinal plants in two areas of Dinajpur district, Bangladesh including plants which can be used as functional foods. Am-Eur J Sustain Agric 2009;3(4):862–76.
[609] Ghani A. Medicinal plants of Bangladesh: chemical constituents and uses. Dhaka: Asiatic society of Bangladesh; 1998.
[610] Rahmatullah M, Khairuzzaman M, Saleem S M, Sattar F, Rahman I, Yesmin M S, et al. Documentation of some folk medicinal practices in Sylhet and Moulvibazar districts, Bangladesh. World J Pharm Pharmaceut Sci 2015;4(8):176–86.
[611] Kawasaki M, Hayashi T, Arisawa M, Morita N, Berganza L H, et al. 8-Hydroxytricetin 7-glucuronide, a β-glucuronidase inhibitor from Scoparia dulcis. Phytochemistry 1988;27(11):3709–11.
[612] Jayaraj P, Mathew B, Parimaladevi B, Ramani V A, Govindarajan R, et al. Isolation of a bioactive flavonoid from Spilanthes calva DC in vitro xanthine oxidase assay and in silico study. Biomed Prev Nutr 2014;4(4):481–4.
[613] Biswas A, Haq W M, Akber M, Ferdausi D, Seraj S, Jahan F I, et al. A survey of medicinal plants used by folk medicinal practitioners of Paschim Shawra and Palordi villages of Gaurnadi Upazila in Barisal district, Bangladesh. Am-Eur J Sustain Agric 2011;5:15–22.
[614] Semwal DK, Semwal RB. Efficacy and safety of Stephania glabra: an alkaloid-rich traditional medicinal plant. Nat Prod Res 2015;29(5):396–410.
[615] Ramya S, Neethirajan K, Jayakumararaj R. Profile of bioactive compounds in Syzygium cumini–a review. J Pharm Res 2012;5(8):4548–53.
[616] Nigam M, Mishra A P, Adhikari-Devkota A, Dirar A I, Hassan M M, Adhikari A, et al. Fruits of Terminalia chebula Retz.: A review on traditional uses, bioactive chemical constituents and pharmacological activities. Phytother Res 2020;34(10):2518–33.
[617] Zheng C J, Li H Q, Ren S C, Xu C L, Rahman K, Qin L P, et al. Phytochemical and pharmacological profile of Vitex negundo. Phytother Res 2015;29(5):633–47.
[618] Liu D, Qu W, Liang J-Y. Flavonoids and other constituents from Alpinia sichuanensis ZY Zhu. Biochem Syst Ecol 2013;46:127–9.
[619] Rahmatullah M, Pk S R, Al-Imran M, Jahan R, et al. The Khasia tribe of Sylhet district, Bangladesh, and their fast-disappearing knowledge of medicinal plants. J Altern Complement Med 2013;19(7):599–606.
[620] Bashar A, Ahmed R, Ahmed I, Jahan R, Ahsan S, Chowdhury H, et al. A survey on the use of medicinal plants by folk medicinal practitioners in three areas of Pirojpur district, Bangladesh. Am-Eur J Sustain Agric 2010;4(2):247–59.
[621] Krishna Chaithanya K, Gopalakrishnan V K, Hagos Z, Kamalakararao K, Noyola P P, John Dogulas P, et al. Isolation and structural characterization of bioactive anti-inflammatory compound mesuaferrin-A from M. Ferrea. Anall Chem Lett, 2019;9(1):74–85.
[622] Esha R T, Chowdhury M R, Adhikary S, Haque K M A, Acharjee M, Nurunnabi M, et al. Medicinal plants used by tribal medicinal practitioners of three clans of the Chakma tribe residing in Rangamati district, Bangladesh. Am-Eur J Sustain Agr 2012;6:74–84.
[623] Singh H, Krishna G, Baske P. Plants used in the treatment of joint diseases (rheumatism, arthritis, gout and lumbago) in Mayurbhanj district of Odisha, India. Rep Opin 2010;2(9):22–6.
[624] Wang L, Jiang Y, Han T, Zheng C, Qin L, et al. A phytochemical, pharmacological and clinical profile of Paederia foetida and P. scandens. Nat Prod Commun 2014;9(6):879–86. doi:10.1177/1934578X1400900640.
[625] Chao W-W, Lin B-F. Isolation and identification of bioactive compounds in Andrographis paniculata (Chuanxinlian). Chin Med 2010;5(1):1–15.
[626] Nenaah G. Antimicrobial activity of Calotropis procera Ait.(Asclepiadaceae) and isolation of four flavonoid glycosides as the active constituents. World J Microbiol Biotechnol 2013;29(7):1255–62.
[627] Sashidhara K V, Singh S P, Srivastava A, Puri A, et al. Identification of the antioxidant principles of Polyalthia longifolia var. pendula using TEAC assay. Nat Prod Res 2011;25(9):918–26.
[628] Ahmmed M R, Ahmed S, Sunny S S I, Kar A, Mahmud S N, Kabir M H, et al. A study on diversity of medicinal plant usage by folk medicinal practitioners in different villages of Dhunat Upazila, Bogra district, Bangladesh. J Pharmacogn Phytochem 2017;6(1):177–86.

[629] Chong Yan LL, Liu Hongju, Lin Zhixin, Chen Panyu, Chen Panyu. Laian Zheng, Study of flavonoids from leaves of Santalum album. China J Chin Materia Medica 2011;36(22):3133.
[630] Kiwon Jung J-SJ, Ahn Mi-Jeong, Kim Chul Young. Preparative isolation and purification of flavonoids from pterocarpus santalinus using centrifugal partition chromatography. J Liquid ChromatogrRelat Technol 2012;35(17):2470.
[631] Syeda Seraj FIJ, Chowdhury Anita Rani, Monjur-EKhuda Mohammad, Khan Mohammad Shamiul Hasan, Aporna Sadia Afrin, Jahan Rownak, et al. Tribal formulations for treatment of pain: a study of the bede community Traditional medicinal practitioners of porabari village in dhaka district, Bangladesh. Afr J Tradit Complement Altern Med 2013;10(1):34.
[632] Roberto F, Vieira RJG, Paton Alan J. Chemical profiling of Ocimum americanum using external flavonoids. Phytochemistry 2003;63(5):567.
[633] Augustine Amalraj SG. Medicinal properties of Terminalia arjuna (Roxb.) Wight & Arn.: a review. J Tradit Complement Med 2017;7(1):78.