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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.

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

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-

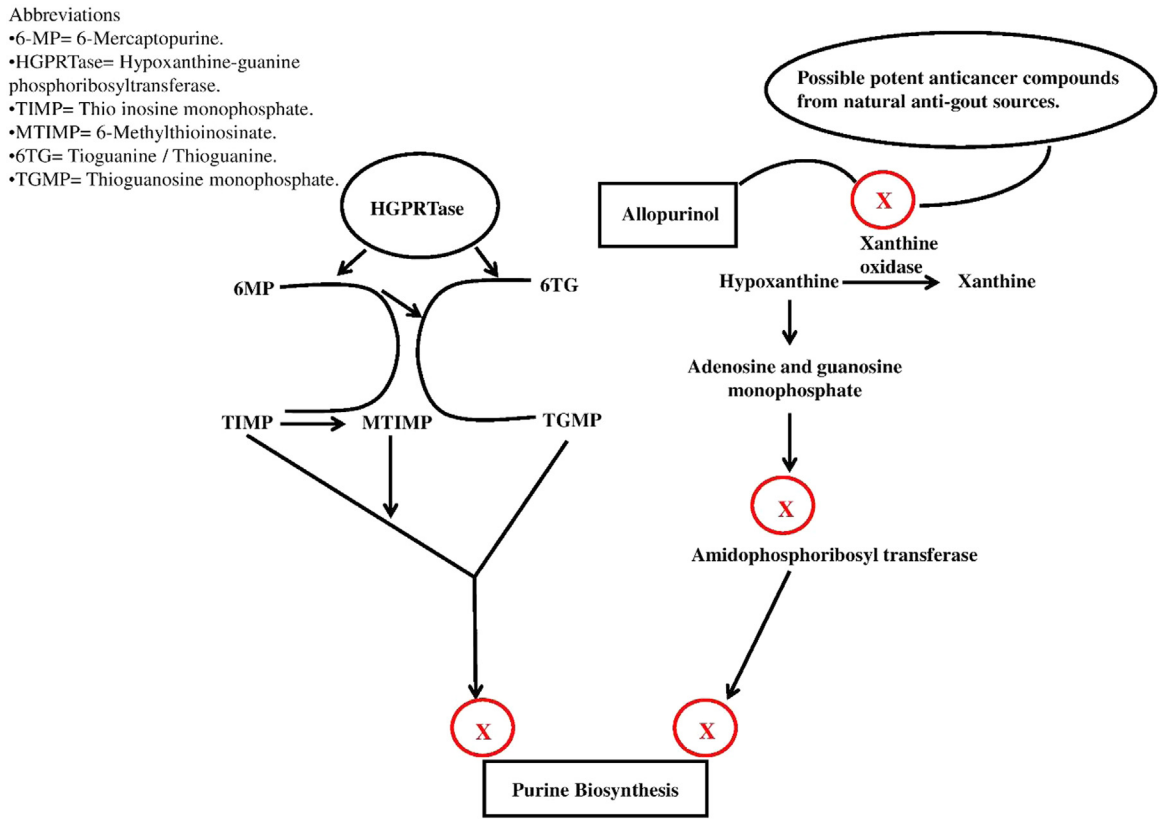

Fig.1. 6-MP and 6TG are transformed into TIMP and TGMP *in-vivo* with the help of HGPRTase enzyme, followed by further methylation of TIMP into MTIMP. TIMP, TGMP, and MTIMP are accumulated intracellularly and inhibit *de novo* purine biosynthesis. On the other side, Allopurinol and hypothetical natural 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

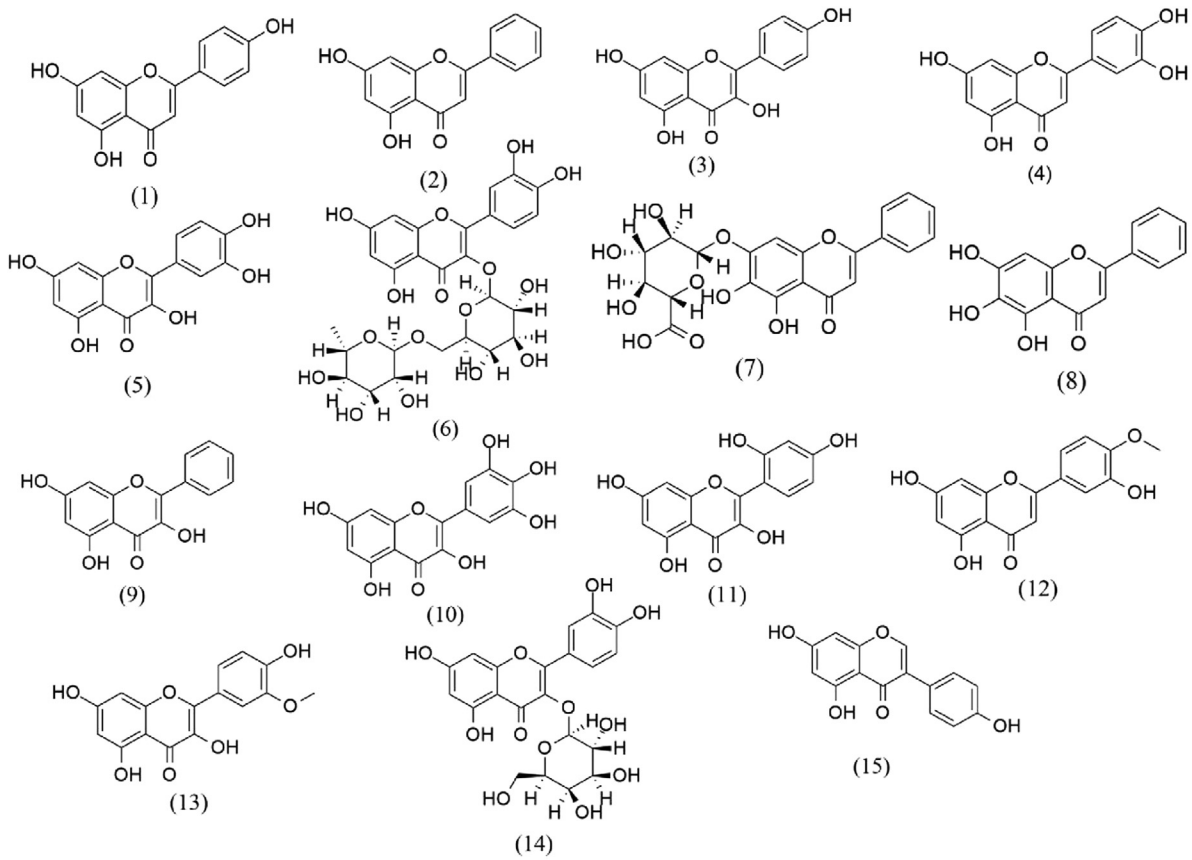

Fig. 2. Structure of discussed flavonoid compounds having cancer chemotherapeutic roles.

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 indicum* 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]

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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, Catechin and epicatechin	[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		[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]

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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]

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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]

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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.

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