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Review Article

Major Bioactive Prenylated Flavonoids from *Humulus lupulus* L., Their Applications in Human Diseases and Structure-Activity Relationships (SAR) – A Review

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Abstract

In recent years, the incidence of cancers, inflammatory diseases, Alzheimer's disease, glucose metabolism disorder and diabetes has increased alarmingly which demands more research into the discovery of new drug candidates to treat these human diseases. Main phytochemicals from *Humulus lupulus* L. (hops) have been demonstrated to have positive impacts on human health, and prenylated flavonoids are one of the major groups of bioactive phytochemicals found in this plant. Thus, this review summarizes the role of major prenylated components in hops in human diseases including cancer, inflammation and viral infections. *In silico* studies of prenylated bioactive compounds against various drug targets such as histone deactylases (HDACs), sirtuins (SIRTs), and acetylcholinesterase (AChE), and the molecular molecular interactions between protein and ligand have also been included. Furthermore, the structure-activity relationships (SAR) studies on these compounds are highlighted. This review concludes that the prenylated phytochemicals from *H. lupulus* L., including xanthohumol (XN), isoxanthohumol (IXN), 8-prenylnaringenin (8-PN) and 6-prenylnaringenin (6-PN), have promising roles in human health and may contribute to new drug discovery and development.

Introduction

The prenylated flavonoids possess prenyl group(s) on the core structure of a flavonoid. Because of prenylation, the lipophilicity of flavonoids increases, and thus, the interaction with the target proteins increases as well. The net result is the enhancement of biological activity. Bioactive prenylated flavonoids have various activities such as estrogenic, immunomodulatory, and anticancer activities.[1] The Cannabaceae is one of the families that produce a large number of prenylated flavonoids. *H. lupulus* of the Cannabaceae has important prenylated flavonoids such as prenylated chalcones[2] and naringenin, and phloroglucinol derivatives such as bitter acids contributing to health benefits.[3]

Humulus lupulus L. (hop) is one of the most significant raw ingredients used in the making of beer and is widely used in many countries.[4] This plant has still been investigated extensively by researchers.[5-7] Before the seventh century CE (common era), historical evidence has indicated that *H. lupulus* L. has been predominantly utilized for medical purposes rather than for the brewing of beer. Therefore, hops or hop cones are well-known in traditional herbal medicine for their therapeutic properties. There has been an increasing interest in the usage of hops in the pharmaceutical industry.[8-9] Figure 1 shows the collected hop cones from Türkiye.

This review focuses on the studies of *H. lupulus* L. prenylated flavonoids. The publications published between 2015 and 2023 in PubMed have been reviewed. The main prenylated flavonoids of *H. lupulus* L. have been indicated

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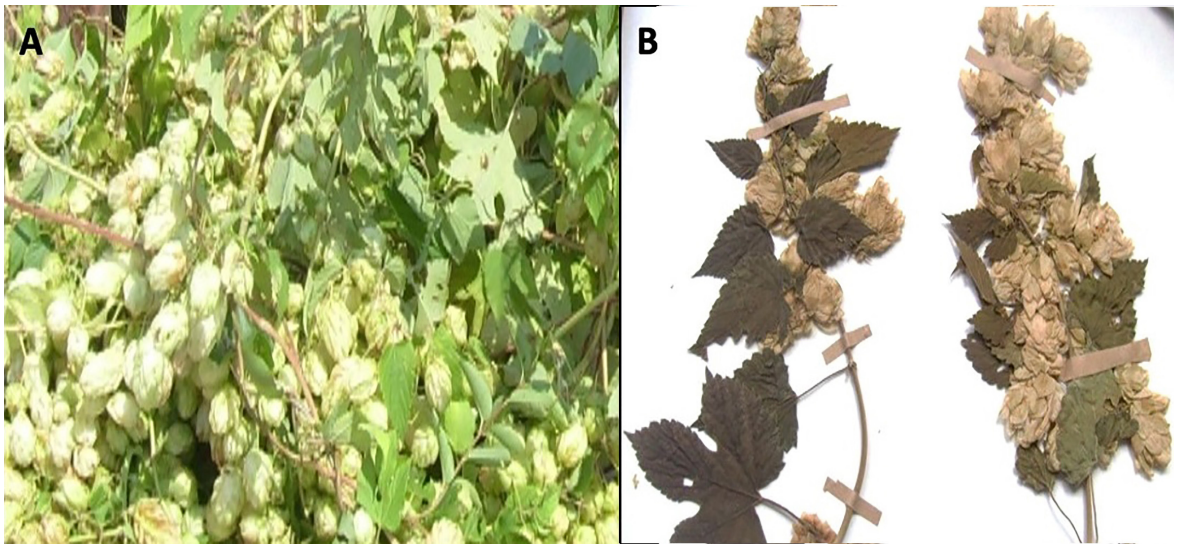

Figure 1. *Humulus lupulus* L. cones. A) collected from Türkiye (Photo by FCO). B) Herbarium image (Photo by Hulusi Malyer).

with their therapeutic values in biological activities such as anticancer, anti-inflammatory, antiviral, antifungal, antimicrobial and etc. *In silico* studies of hop components against various drug targets have also been reviewed. In addition, the prenylated components with the contribution of functional groups have been shown in this review.

Major Components of Hops

Both clinical and epidemiological investigation on the hop plant has become more prevalent due to the health-promoting elements that can greatly lessen the worldwide socioeconomic burden brought on by cancer and cardiovascular diseases and contribute to our understanding of the disease processes.[10] We investigated hop extracts for their biological activities in our previously reported studies.[11-12] The investigations have afforded the isolation and identification of pharmacologically significant substances like flavonoids, flavanones, chalcones, and derivatives of phloroglucinol.[13] The hop flowers have received a lot of interest as a potential source of beneficial small molecules for human health including humulone, lupulone, isohumulone, and xanthohumol (XN) that are known to have antibacterial, anti-inflammatory, anticancer, and antioxidant effects.[14] Hop bitter acids such as phloroglucinol compounds have anticancer properties, and depending on their chemical composition may be divided primarily into two categories: the α-acids (humulone, cohumulone, adhumulone etc..) and β-acids (lupulone, colupulone, adlupulone etc..). The level of bitter acids in hops is directly associated with its resistance to diseases including hop stunt virus, downy mildew, verticillium wilt, and hop mosaic virus. Additionally, it has been reported that hop extracts containing bitter acids have been used for antibacterial therapies.[15] The hop plant also contains several prenylated flavonoids including isoxanthohumol (IXN), desmethylxanthohumol (DMX), 6-geranylnaringenin (6-GN), 8-prenylnaringenin (8-PN), and 6-prenylnaringenin (6-PN). XN is the most significant hop flavonoid, which has been used in the treatment and prevention of several diseases, including cancer.[14,16-17] The structures of hop components are given in Figure 2.

Biological Activities of the Main Prenylated Flavonoids of Hops

In recent years, the biological functions of hops have been the subject of multiple investigations. This section will cover the biological activities of hops including anti-inflammatory, anticancer, anti-Alzheimer, antiviral, antidiabetic, antimicrobial, and antifungal activities. Figure 3 exhibits an illustration of the treatment of the related human diseases with hop bioactive components.

Anticancer activity

Numerous studies reported that XN induced cancer cell death and inhibited tumour growth *in vitro* and *in vivo*.[3] The effect of XN was shown in various human cancers such as estrogen receptor-positive breast cancer cells (MCF-7),[18-20] ovarian (A2780), colon (HT-29), cervical cancer,[21,22] lung,[22,23] melanoma and hepatocellular,[24,25] and prostate (DU145, PC-3).[26-28] The function of tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL) in human prostate adenocarcinoma cells (LNCaP) cells was induced and resulted in the expression of caspases-3, -8, -9, Bid and Bax.[27] XN inhibits the phosphorylation of the signal transducer and activator of transcription3 (STAT3) and the expression of its downstream target genes cyclinD1, surviving, and Bcl. It induced apoptosis in various PC cells such as Panc1 and BxPC3. As a result, XN can be used as a promising therapeutic agent.[27,29] Angiogenesis was inhibited by blocking NF-κB activation in PC cells in *in vitro* and *in vivo* studies by XN treatment. As a result, XN suppressed vascular endothelial growth factor (VEGF) expression and IL-8 in PC cell lines.[28] XN was investigated for its potential anticancer activity and mechanism in LSCC (laryngeal squamous cell carcinoma) for the first time.[30,31] XN affected cell viability in RK33 and RK45

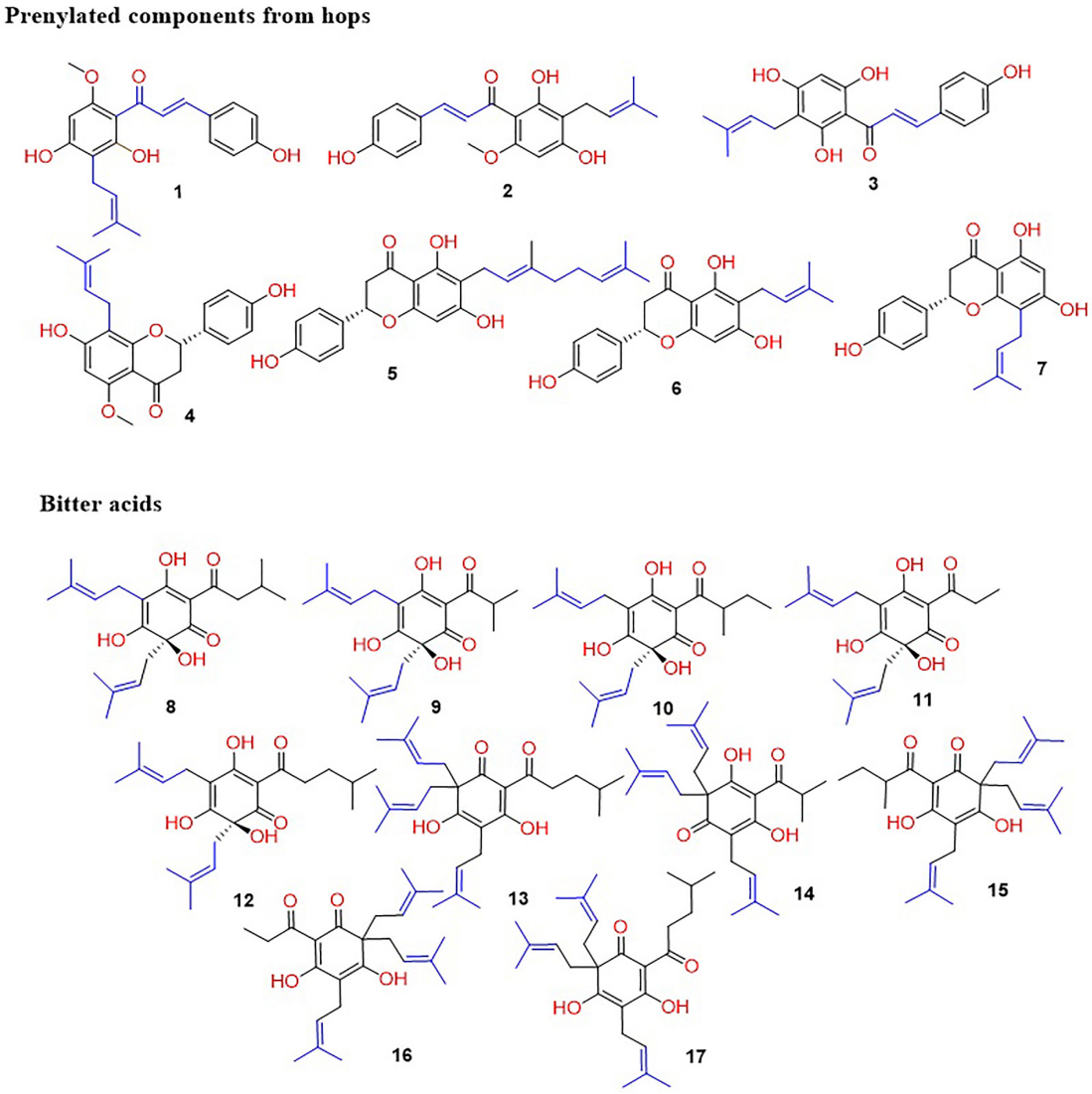

Figure 2. The chemical structures of main prenylated flavonoids of hops. **(1)** Xanthohumol (XN) **(2)** Naringenin **(3)** Desmethylxanthohumol (DMX) **(4)** Isoxanthohumol (IXN) **(5)** 6-Geranylnaringenin (6-GN) **(6)** 8-Prenylnaringenin (8-PN) **(7)** 6-Prenylnaringenin (6-PN) **(8)** Humulone **(9)** Cohumulone **(10)** Adhumulone **(11)** Posthumulone **(12)** Prehumulone **(13)** Lupulone **(14)** Colupulone **(15)** Adlupulone **(16)** Postlupulone **(17)** Prelupulone.[14-17]

laryngeal cancer cells and normal cells (OLN-93).[30] Treatment of A549 and H1563 lung cancer cells with XN caused up-regulated tumour suppressor proteins (p53 and p21) and down-regulated cyclin D1. Thus, it was suggested that XN could play a role as a promising anticancer drug candidate against lung carcinomas.[30] Furthermore, the cell viability was dramatically decreased in HT-29 cell line by XN with IC_{50} of 10 μM.[32] According to cell cycle analysis in HT29 cell line, XN was arrested in G2/M phase, and it suppressed cyclin B1 and Ras/MEK/ERK pathway.[32] It was reported that cell proliferation in HL-60 leukaemia cells was significantly inhibited by XN, however, it did not cause cleavage or apoptosis of the caspase-3.[33] It was indicated that treating U87 MG cells with XN inhibited the IGFBP2/Akt/Bcl2 that was mediated by activation of miR-204-3p and decreased the cell viability.[34] Guo *et al.*[35] in their study, reported that treated SGC-7901 cells with 10 μg/mL of XN for 72 h contributed to apoptosis approximately 40%. In addition, XN (1 mg/kg) administered intraperitoneally for 3 weeks significantly reduced the growth of tumour volume in BALB/c mice. Furthermore, XN down-regulated the anti-apoptotic proteins Bcl-XL and Bcl-2, and up-regulated the proapoptotic proteins Bax, Bid, PARP and caspase-3. The phosphorylation of PI3K/Akt/mTOR in SGC7901 cells was induced by XN.[35] The ERK1/2-Fra1-cyclin D1 pathway was affected in XN-treated cells such as lung cancer cells (HCC827, H1975 and H23).[32] In addition, XN reduced the tumor growth in HCC827 xenograft model.[36] It has been reported that XN sensitizes colorectal cancer cells to inhibit cell proliferation and DNA damage and apoptosis in CRC cells for chemotherapy.[37,38] The effect of XN, a polymethoxyflavone, and nobiletin in colorectal cancer stem cells was proposed for its adjuvant potency in cancer therapies. Then, it is determined that

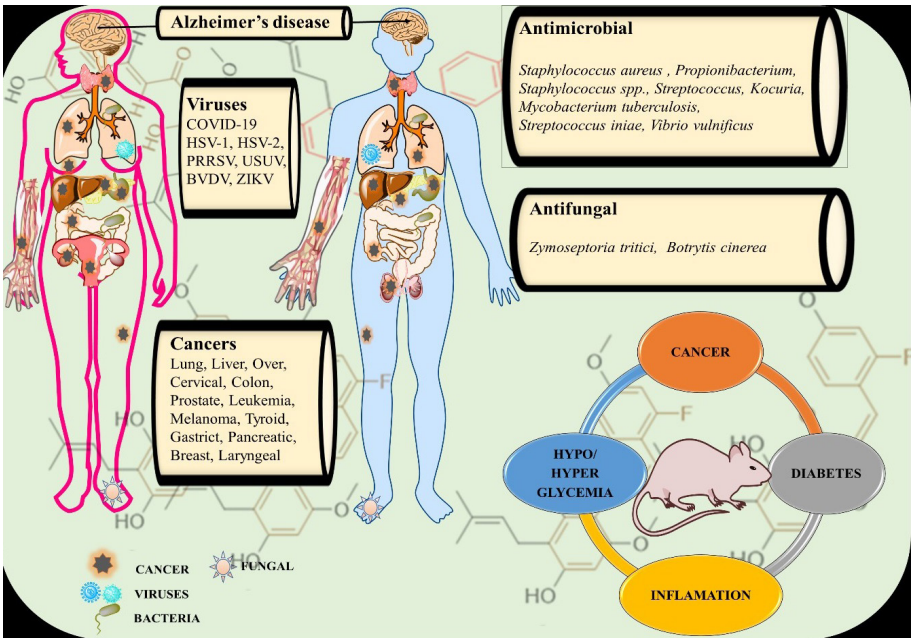

Figure 3. A schematic overview of the components in the related human diseases.
Coronavirus (COVID 19); Porcine reproductive and respiratory syndrome viruses (PRRSV); Usutu virus (USUV); Zika virus (ZIKV); Bovine viral diarrhea virus (BVDV); Herpes viruses (HSV1 and HSV2).

this mixture can suppress the migration of cancer stem cells, and reduce CD44v6 expression.[39] It was also reported that XN containing nobiletin sensitized colorectal cancer stem cells to 5-fluorouracil and oxaliplatin.[39] In a study, the treatment with XN (50 μM) for 24 hours on U87 glioma cells caused a decrease in cell proliferation (62.2% ± 3.7), and this resulted in a decrease in cell death (33.7% ± 0.9). It also reported that XN induced autophagy and thus, inhibited the Akt/mTOR/S6K pathway, and promoted the formation of LC3-II and p62 degradation.[40] STIM1 signaling inhibited through miR-4725-3p in glioma cells.[41] Furthermore, XN induces the expression levels of miR-204-3p to transcriptionally regulate the ERK/c-Fos signalling pathway.[34]

XN could inhibit cell viability and induce apoptosis as dose-dependent, and it affected the cell cycle of MCF-7/ADR cells. As a result, XN was reported as a promising compound for doxorubicin-resistant breast cancer cells.[19] It was mentioned for the first time, XN had the ability to sensitize colon cancer cells SN38 as an anticancer agent.[37] It was reported that XN inhibits cell proliferation, induces apoptosis, and suppresses metastasis of AGS cells.[42] It was shown that XN reduced cell proliferation in TPC-1 cancer cells with a concentration of 10 μM. At a concentration of 100 μM, a decrease in cell viability was determined by inducing apoptosis. Therefore, it is believed that XN is a high potential candidate for the treatment of thyroid cancer.[43] In a reported study, XN has been investigated in mouse models and *in vitro* against various cancer cells including H520 and H358 cells.[44] It was shown that XN reduced the expression of GATA3 in mice, whereas it activated STAT4 and T-bet in Th cells.[45] Two enzymes of the AKR superfamily members are important pharmacological targets for cancer (AKR1B10) and diabetic complications (AKR1B1) treatments. The inhibitory potentials of the AKR superfamily (AKR1A1, AKR1B1 and AKR1B10) were investigated. According to these findings, XN, IXN, and 8-PN are potent inhibitors of AKR1B1 and AKR1B10.[46] IXN was investigated *in vitro* in melanoma cell line B16-F10 and *in vivo* in a metastatic model. According to the results, It was observed that XN derivative, IXN decreased the cell viability in melanoma cells dependent on a dose.[47]

Although 8-PN induced the levels of P450 1A1/B1 mRNA in MCF7 cells, 6-PN inhibited P450 1A1 levels at 0.6 μM and for 1B1 at 0.2 μM. XN at 0.28 μM showed the 1A1 inhibitor activity than IXN at 1.6 μM.[48,49] More importantly, XN has proved to exhibit cytoprotecting due to its ability to induce endogenous antioxidant defence molecules. Overall, the biological results concluded that XN had an excellent inhibitor potential in most cancer types. It is also given in Table 1. Interestingly, it is shown in Figure 4 that XN modulates these multiple molecular pathways leading to the inhibition of cancer features such as inflammation, cell cycle arrest, angiogenesis, apoptosis, proliferation, invasion and migration in various cancers. As a result, due to its antitumor potency and nontoxic properties, XN could be a promising drug candidate for further cancer therapy studies.

Anti-inflammatory activity

Inflammation is a process in the human body that involves inflammatory regulators such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, nitric oxide (NO), and reactive oxygen species (ROS). XN was determined with its inhibition activity of TNF-α, IL-1β, and NO, and activation of NF-κB signaling.[50] It is thought that the effect of XN on the regulation of NRF2 signalling could be a promising

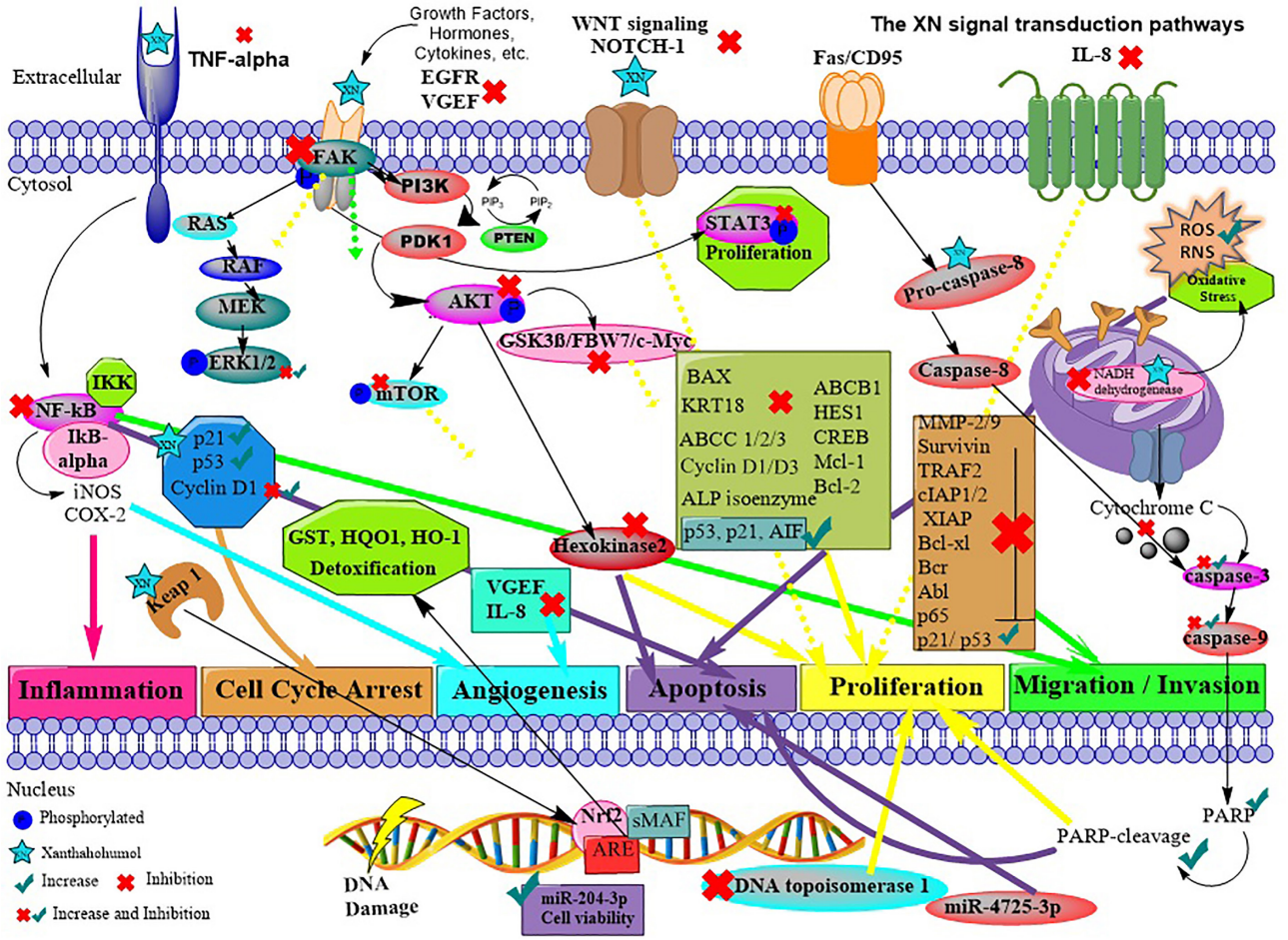

Figure 4. The metabolic pathway of XN (Redrawn).
XN: Xanthohumol; Signal transducer and activator of transcription 3 (STAT3); Epidermal growth factor receptor (EGFR); Focal adhesion kinase (FAK), Glycogen synthase kinase-3 beta, (GSK-3β); Tumor necrosis factor alpha (TNF-alpha); Glutathione S-transferases (GST); Nuclear factor erythroid 2-related factor 2 (Nrf2); antioxidant response element (ARE); Heme oxygenase 1 (HO-1); NAD(P)H quinine oxidoreductase (HQO-1); small musculoaponeurotic fibrosarcoma oncogene homologue (sMAF); Inhibitor of nuclear factor kappa-B kinase subunit (IKK); Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBα); Mammalian target of rapamycin (mTOR); Phosphoinositide 3-kinases (PI3K); Pyruvate dehydrogenase lipoamide kinase isozyme 1 (PDK1); Phosphatase and tensin homolog (PTEN); Protein kinase B (AKT); F-box and WD repeat domain-containing 7 (FBW7); Neurogenic locus notch homolog protein 1 (Notch1); Bcl-2 Associated X-protein (BAX); Keratin 18 (KRT18); Induced myeloid leukemia cell differentiation protein (Mcl-1); cAMP response element-binding protein (CREB); B-cell lymphoma 2 (Bcl-2); ATP-binding cassette sub-family B member 1 (ABCB1); Matrix metallopeptidase (MMP); TNF receptor associated factor2 (TRAF2); Cellular inhibitor of apoptosis protein 1 (cIAP1); Apoptosis Inducing Factor (AIF); B-cell lymphoma-extra-large (Bcl-xL); Cluster region protein (BCR); Tyrosine-protein kinase (ABL); Mitogen-activated protein kinase kinase kinase (MEK); Extracellular signal-regulated kinase (ERK); Inducible nitric oxide synthase (iNOS); Cyclooxygenase 2 (COX-2); X-linked inhibitor of apoptosis protein (XIAP); Poly (ADP-ribose) polymerase (PARP); Nuclear factor kappa light chain enhancer of activated B cells (NF-κB); Vascular Endothelial Growth Factor (VEGF); Interleukin-8 (IL-8); hes family bHLH transcription factor 1 (HES1); Cluster of differentiation 95 (CD95); Kelch-like ECH-associated protein 1 (Keap 1); Reactive oxygen species (ROS); Reactive nitrogen species (RNS); Nicotinamide adenine dinucleotide hydrid (NADH).

Table 1. XN and IXN related doses and their actions in different cancer types.

Cancer Type	Cell Line/Animal Model	Action	Dose	Ref
Breast	BALB/c mouse tumor model	Suppression of tumor growth, ↓tumor weight ↓survivin ↑caspase cleavage ↓Notch-1 ↓Ki-67		20
	Adriamycin-resistant MCF-7	↓Cell viability ↑radio and chemosensitivity ↑Apoptosis ↑γ-H2AX ↓STAT3 ↓MDR1 ↓EGFR	10 μM	19
Colorectal	Xenograft mouse model FHC, SW620, LOVO, CCD841, SW480, CoN, HT29, HCT116, CDD-18Co	↓tumor cell proliferation ↑Apoptosis ↑cyt.c release ↓cell viability ↓cell cycle arrest ↑Apoptosis ↑caspase-3 ↑caspase-9 ↓cyclin B1 ↓MEK/ERK	10 and 100 μM	32,37
	Male Sprague Dawley rats by using SW480 CRC cells	↓tumor cell proliferation↑ Apoptosis ↓Wnt/β-catenin signaling ↓Bax ↓ Bcl-2 ↓caspase-3 ↓iNOS ↓COX-2		38

Table 1. Continued.

	FHC, CCD841, CoN, HT29, SW480, LOVO, HCT116 and SW620	↓cell proliferation, cell viability, and colony formation ↑Apoptosis ↓HK2 ↓glycolysis ↓EGFR-Akt	25 μM	32
	HCT116 and RKO CRC cell line	↓ CD44v6 ↓S and G2/M ↑cell death-related genes ↓cell viability of CRC stem cells	5–10 and 25 μg/mL	39
Cervical	Ca Ski	↓proliferation ↑Apoptosis ↑caspase-3 ↑caspase-8 ↑caspase-9 ↑cell cycle arrest ↑p53 ↓XIAP	59.96 μM	22
Cholangiocarcinoma	KKU-M139 and KKU-M214	↓cell growth ↓STAT3	20 and 50 μM	29
Laryngeal	RK33 and RK45	↓cell viability ↑Apoptosis ↑caspase-3 ↑caspase-8 ↑caspase-9 ↑p53 ↑p21 ↓cyclin D1 ↓ERK1/2	12.3 and 22.5 μM	30
	SCC4	↓proliferation ↑Apoptosis ↑PARP ↑p53 ↑AIF ↓Bcl-2 ↓Mcl-1	20, 30, 40 μM	31
Thyroid	TPC-1 cell lines	↓TPC-1 cell proliferation. induce cell death, DNA fragmentation and promotes cell cycle arrest in S phase ↑caspase-3,-7 activity, support pro-apoptotic effect	10 μM	43
Glioblastoma	U87 glioblastoma	↓cell viability ↑Apoptosis ↓IGFBP2/Akt/Bcl-2 ↑mIR-204-3p ↑ERK/c-Fos	25 μM	34
	Human glioblastoma U87-MG	↑miR-4725-3p ↓cell viability ↓STIM1 signaling	10 and 20 μM	41
Hematological	HL60	Activation of p38 MAPK	1-50 μM	33
Pancreatic	BxPC3, MXPaCa2, and AsPC1	↓ cell proliferation ↓NF-Kb ↓VGEF ↓IL-8 ↓mRNA	0.5–25 μmol/L	28
	PANC1 and BxPC3	↓proliferation, viability, colony formation ↑Apoptosis ↓p-STAT3	5–100 μM	26
	Subcutaneous xenograft mouse model by using BXPC-3 cells	↓tumor growth and angiogenesis ↓NF-κB activation ↓tube formation ↓VGEF ↓IL8	10 mg/kg/ week	28
Liver	Huh7, Hep3B, SK-Hep1, and HepG2	↓colony formation, cell viability and confluency ability ↓HES1 ↓Notch1 pathway	5 μM	25
Lung	Xenograft mouse model by using HCC827 cells	↓tumor growth ↓Cyclin D1 ↓ERK1/2-fra1	10mg/kg (i.p.),	36
	A549	Nuclear apoptotic features ↑activity of caspase-3, -8, and -9.	5–50 μM	21
	In vitro and xenograft mouse models using A549, H520 and H358 cell line	Suppressed cell viability, colony formation and induced apoptosis inhibited Akt activity, suppressed NSCLC is xenograft tumor growth ↑PUMA expression in tumor tissues	10 mg/kg (i.p.)	44
Prostate	LNCaP combination with TRAIL	↑caspases-3, -8, and ↑Bax ↓ Bcl-xL	10 μM	27
Melonoma (IXN)	B16-F10 *in vivo* in a murine metastatic model	↓ Melanoma cell viability suppression of the processes that define metastasis–cell adhesion, invasion, and migration	30 μM	47
Gastric	GC cells (AGS, SGC-7901, MGC-803), GES-1	GC cell viability ↓Bcl-2 activity ↑Bax activity inhibition of NF-κB signaling, ↓ROS overproduction	1–100 μM	42

Xanthohumol (XN); Iso-xanthohumol (IXN); Signal transducer and activator of transcription 3 (STAT3); Multidrug Resistance Mutation (MDR1); Epidermal growth factor receptor (EGFR); Cytochrome c (cyt.c); extracellular signal-regulated kinase (ERK); Inducible nitric oxide synthase (iNOS); Cyclooxygenase 2 (COX-2); X-linked inhibitor of apoptosis protein (XIAP); Poly (ADP-ribose) polymerase (PARP); insulin like growth factor binding protein 2 (IGFBP2); Mitogen-activated protein kinase (MAPK); nuclear factor kappa light chain enhancer of activated B cells (NF-κB); Vascular Endothelial Growth Factor (VEGF); Interleukin-8 (IL-8); hes family bHLH transcription factor 1 (HES1); Non-small cell lung cancer (NSCLC); tumor necrosis factor-related apoptosis-inducing ligand (TRAIL); Reactive oxygen species (ROS); GC (gastric cancer)

strategy for the progression of inflammation-related neurodegenerative diseases.[51]

To understand the role of bioactive components isolated from hop extracts, these compounds were tested in various models.[52] Related to the immune system and the inflammatory process, XN and IXN were identified as potential for their anti-inflammatory activities.[52] The *in vivo* anti-inflammatory role of XN was assessed in models of acute and chronic inflammation in different organs. Oxazolone-induced dermatitis was prevented by topical application of XN,[53] and also hop components were reported with biomaterial applications such as skin

wound healing and regeneration.[54] Also, it was reviewed the inhibitor effect of XN on pro-inflammatory enzymes such as COX-1 and COX-2.[54] When the antiinflammatory activity of hops extracts was characterized in an *in vitro* model of gastroenteritis, identified active compounds that inhibited IL-8 release in human gastric epithelial AGS cells in a dose-dependent manner. Depending on the phytochemical analysis it was revealed that XN-A and XN-D were determined as the main active ingredients.[55] Hydroalcoholic extract of hops inhibited IL-8 release in a dose-dependent (IC_{50} = 3.95 µg/mL). This result indicated that this extract showed a strong inhibitory effect owing to prenylated chalcone content.[56] According to one of the reported studies on 14 healthy volunteers, XN through diet was observed for its anti-inflammatory effects.[56] Additionally, it is hypothesized that XN may reduce the immune response in humans to lipoteichoic acid at low doses. Therefore, these effects might be related to the binding or uptake of XN by monocytes.[56]

Consequently, the studies reveal that XN has an anti-inflammatory effect. Its broad-spectrum activity is effective in the treatment of various diseases associated with inflammation.

Anti-Alzheimer activity

The formation of arachidonic acid (AA) in the brain is regulated by monoacylglycerol lipase (MAGL) that terminates the endocannabinoid 2-arachidonoylglycerol (2-AG) signalling.[57] As a result, monoacylglycerol lipase (MAGL) plays a dual role in controlling brain inflammation by regulating arachidonate and endocannabinoid concentrations.[58] In this context, the natural product (NP-2) showed an inhibitor activity (IC_{50}= 9.5 ± 1.2 µM) against hMAGL. The study was determined with an inhibitor (NP-2 and/or 8-PN) of hops.[59] Alzheimer's disease (AD) is characterized by neuroinflammation associated with common neuronal death.[60] It has been reported that NPs possess inhibition effects of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which are important enzymes of AD. In a study reported by Orhan *et al.*[61], it was investigated that hop components including XN and acyl phloroglucinol derivatives (compounds 1-14) may have an inhibitor activity to AChE and BChE. As a result, 3-hydroxy-XN with IC_{50} value of 51.25 ± 0.88 µM and XN with IC_{50} value of 71.34 ± 2.09 µM were determined in a moderate potency against AChE. In addition to 3-hydroxy-XN with IC_{50} of 63.07 ± 3.76 µM and XN with IC_{50} of 32.67 ± 2.82 µM, 8-PN with IC_{50} of 86.58 ± 3.74 µM also exhibited inhibition activity towards BChE in the micromolar ranges. Thus, XN was identified with its highest inhibition potential compared to reference drug galantamine (IC_{50} = 46.58 ± 0.91 µM). Consequently, these results demonstrate that XN may be a potential candidate for the discovery of new cholinesterase inhibitors for the treatment of AD.

Antiviral activity

Coronavirus (called SARS-COV-2 or COVID 19) has infected millions of people since 2019 worldwide. However, the identified hop stunt viroid (HSVd)[62], apple fruit crinkle viroid (AFCVd)[63], citrus bark cracking viroid (CBCVd)[64], and hop latent viroid (HLVd)[64] caused hop diseases.[62-64] For instance, Lin *et al.*[65] reported with IC_{50} value of 1.53 µM of XN as pan-inhibitors of the main protease of COVID-19. Furthermore, XN showed the inhibition activities against several viruses such as porcine reproductive and respiratory syndrome viruses (PRRSV).[66,67] XN was found as a promising therapeutic agent on 15 µM for PRRSV. Liu *et al.*[67] showed that XN could reduce oxidative stress of PRRSV-induced.8-PN showed an antiviral effect against influenza virus which provides the inhibition of replication in the changing range (IC_{50} = 5.5 ± 0.2) according to virus types.[68] Both XN and eeyarestatin I have been reported to suppress replication of Usutu virus (USUV) and Zika virus (ZIKV) but eeyarestatin I has demonstrated a stronger antiviral effect than XN.[69] In addition, IXN is one of the other prenylflavonoids that affect bovine viral diarrhea virus (BVDV), herpes viruses (HSV1 and HSV2).[70]

Antidiabetic activity

Disruption of glucose metabolism leads to several human diseases such as diabetes mellitus (Type1 and Type2), hyper- and hypoglycemia, and obesity. Although there have been many studies conducted until 2015, the researchers continue to understand the effect potentials of hop components. For instance, one of the studies demonstrated that body weight for obese C57BL/6J mice was lost by XN (0, 30, 60 mg/kg weight/daily amount of XN for 12 weeks).[71] Hop components XN, IXN and 8-PN are potential uncompetitive inhibitors of aldo-keto reductase superfamily members of AKR1B1 and AK1B10.[46] KDT501 is a novel isohumulone, reduces weight, and insulin resistance, and dyslipidemia *in vivo*.[72] In recent years, 8-PN and naringenin (50 mg/kg) have improved islet dysfunction and glucose homeostasis in streptozotocin (STZ)-induced insulin-deficient diabetic mice with oral administration.[73] XN has a protective effect against type-2 diabetes-induced liver fibrosis and steatosis via NRF2/AGE/RAGE/NF-κB signalling in nonalcoholic fatty liver disease (NAFLD) rat model.[74] XN was used as a glucose/fructose transport inhibitor agent in a study on glucagon-like peptide.[75] The IC_{50} values of 8-PN (45.92 µM, >100 µM, >50 µM) and 8-GN (3.77 µM, 15.38 µM, >50 µM) were determined against α-glucosidase, α-amylase, and β-glucosidase, respectively.[76] In a study, the binding affinities of 8-PN and 8-PG have been reported by using the Microscale Thermophoresis analysis as Kd value of 4.1 ± 1.2 µM, and 7.4 ± 3.5 µM, respectively, against His-tag-labeled hlGP which is associated with type2 diabetes protein.[77]

Antimicrobial activity

The discovery of new drugs with strong antimicrobial

activity, especially against resistant strains, is very important.[78] For this reason, hop, which has a long history in traditional medicine, has been used as a treatment for many conditions including bacterial infections, as well as for its protective properties.[78,79] It is known that prenylated flavonoids have been proven to have strong antimicrobial activity.[80,81] Prenylflavonoids, especially XN was reported in an earlies study with antibacterial activity against Gram-positive bacteria such as *Staphylococcus*, *Propionibacterium*, *Kocuria*, and *Streptococcus*[82] XN, chalconaringenin, and naringenin were shown to inhibit the growth of *S. aureus*.[83] *Staphylococcus* spp. were reduced by humulone, lupulone and XN. As a result, the strongest effect was obtained by lupulone after XN. Lupulone (~125 µg/mL) and XN (~60 µg/mL) at high concentrations reduced the number of surviving bacterial cells to zero.[84] It has been reported that lupulone exhibits an inhibitor effect against the growth of methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* with MIC values for DMX (0.6-1.2 µg/ml and 19.5-39 µg/mL).[85] XN and lupulone showed strong antibacterial properties among the studied compounds.[86] Lou *et al*.[87] investigated the combined effect of XN with isoniazid against mice infected with *Mycobacterium tuberculosis*.[87] In another study, the antimicrobial activities of hops were investigated against *Streptococcus iniae* and *Vibrio vulnificus*. It has been reported that XN shows the strongest antibacterial property against *Streptococcus*.[78]

Antifungal activity

The antifungal activity of prenylflavonoids has been revealed in various studies; for instance, antifungal activity against *Zymoseptoria tritici* was determined by cohumulone and DMX with half-maximum inhibitory concentrations of 0.11 and 0.2 g/L, respectively.[88] It was demonstrated that IXN significantly inhibited antifungal activity against *B. cinerea* with an EC_{50} value of 4.32 µg/mL. This study shows that IXN can be used for phytopathogenic fungi.[89]

In Silico Studies

To analyze the effects of inhibitor candidates against drug targets, computer-assisted approaches led to experimental studies.[90] According to the reported studies, XN, 6-PN, and 8-PN have been evaluated to understand their binding affinities against acyl-protein thioesterase 2.[91] In one of the reported studies, Many flavonoids were investigated against SIRT1 by molecular docking study to understand their interactions to select effective and potent flavonoid candidates. Among these flavonoids, XN was mediated by the activation of SIRT1 and had hepatoprotective effects.[92] Therefore, among the reported flavonoid compounds, XN displayed the docking score of -5.26 kcal/mol against SIRT1. However, SIRT1 activator STAC showed the lowest docking score -6.20 kcal/mol.[92] As shown in Table 2, among the *in silico* results of an FDA-approved drug, it was notable that in an earlier reported study, a selective SIRT1 inhibitor, selisistat (EX527) exhibited strong interactions such as hydrogen binding and pi-pi interactions with Gln345, and His363 and Phe273, respectively.[93] The redocking of selisistat and the 2D interactions including structural water molecules and Phe273, Phe297, Ile279, Ile316, Ile411, Ile347, Asp348, Gln345 have been reported in the recent study,[94] and the docking score was calculated as -7.78 kcal/mol.[95] Moreover, it was reported that selisistat showed more hydrophobic interactions with SIRT6 including H131, W186, F62, Q111, T213 residues than SIRT1 in the active pocket of the protein.[96]

In a study with GOLD algorithm, 6-PN and 8-PN showed inhibitory activity against HDAC enzymes calculated as HDAC2 (62.8 kcal/mol), HDAC4 (66.5 kcal/mol) HDAC7 (56.9 kcal/mol), HDAC8 (59.5 kcal/mol) for 6-PN and HDAC2 (37 kcal/mol), HDAC4 (57.6 kcal/mol), HDAC7 (56.7 kcal/mol), HDAC8 (64.8 kcal/mol) for 8-PN.[97] Taken together, based on the *in silico* data both 6-PN and 8-PN were suggested to exhibit inhibitory activity against HDAC enzymes of class I and II comparable to standard HDACi such as naturally identified and biologically active TSA (trichostatin A) and FDA-approved drug SAHA (Vorinostat).[97] Among the *in silico* results of an FDA-approved drug, HDAC2 inhibitor, SAHA has the LibDock score and binding energy as −126.37 kcal/mol and -33.25 kcal/mol, respectively. It was shown that the hydrogen bond interactions with Arg39, His183, Gly305, Gly154 amino acids and pi-pi interaction with Phe155.[98,99] The affinity score of SAHA was compared with similar analogue.[100] SAHA was reported for four with His18, Gly27, Lys31 and Lys331 and five hydrogen bonds with Asp104, His145, His146, Asp181 and Tyr208 to HDAC1 and HDAC2, respectively. For HDAC4 and HDAC6, SAHA showed hydrogen bond interactions with His802, Asp840 and His842, and Gly582 and His614, respectively.[101] The binding energies of SAHA for HDAC2 (−20.884 kcal/mol and −8.287 kcal/mol) and HDAC6 (−20.231 kcal/mol and −10.664 kcal/mol) were determined. Also, it was found as −17.547 kcal/mol and −11.064 kcal/mol for TSA drug for HDAC6.[102] In one of the reported studies, the estimated binding free energy of SAHA for HDAC8 was calculated as −4.35 kcal/mol.[103] Docking score of SAHA against HDAC2 was found as −7.068 kcal/mol by MOE software.[104] Furthermore, in one of the reported studies, SAHA was compared with naturally occurring components including apigenin, flavone, and luteolin against HDAC1 and HDAC2.[105] Molecular docking simulation results showed that the studied components exhibited lower binding energy with focused docking compared to reference molecule SAHA-HDAC1 (-8.46 kcal/mol) and HDAC2 (-8.45 kcal/mol).[105] On the contrary of focused docking, the free energy of interaction results for blind docking were reported as -7.23 kcal/mol and -7.45 kcal/mol for HDAC1 and HDAC2, respectively. Thus, the best interaction energy was found for flavone and apigenin with the specific residues.[105] In another study, the docking score of TSA-HDAC6 by the Glide method was determined as -8.782 kcal/mol, and the interaction for TSA was reported with Phe643 in an earlier study.[106,107] The docking scores and interactions are given

in Table 2.

IFD and GOLD molecular docking protocols were applied to confirm the catalytic binding energies of XN against cholinesterases, AChE and BChE.[61] According to docking results, 8-PN showed a binding energy of -8.86 kcal/mol with BChE. H-bond and π-π interactions were observed between 8-PN and specific amino acid residues including Gly117, His438, and Ser198 of BChE. It was also supported by *in vitro* analysis (IC_{50} = 86.58 ± 3.74 μM). Whereas, 8-PN showed no significant inhibition of AChE, but moderately inhibited plasma cholinesterase (IC_{50} = 86.6 μM).[108] Natural product dihydroquercetin was studied against AChE and BChE.[109] FDA-approved inhibitors such as donepezil, galantamine, and rivastigmine are used in the treatment of Alzheimer's disease. Donepezil is used to inhibit the hydrolysis of AChE, and is a noncompetitive

Table 2. The docking scores and molecular interactions of XN, 8-PN, and the inhibitors of drug targets.

Compounds	Docking score, binding free energy (kcal/mol) against AChE	Target	Specific amino acid residues	Interactions	Ref.
XN	-5.26	SIRT1	-	-	92
STAC (activator)	-6.20	SIRT1			92
Selisistat (EX527)	-7.78	SIRT1	Gln345, His363 Phe273 Phe297, Ile279, Ile316, Ile411, Ile347, Asp348,	H-bonds, pi-pi	93-96
8-PN	HDAC2 (62.8), HDAC4 (66.5) HDAC7 (56.9), HDAC8 (59.5) for 6-PN and HDAC2 (37), HDAC4 (57.6), HDAC7 (56.7), HDAC8 (64.8) for 8-PN (GOLD program)	HDACs			97
SAHA	126.37 (LibDock) -33.25, -8.46, -7.23	HDAC1	Arg39, His183, Gly305, Gly154, Phe155, His18, Gly27, Lys31 and Lys331	H-bonds, pi-pi	98-100, 105
SAHA	−20.884 and −8.287 −7.068, -8.45, -7.45	HDAC2	Asp104, His145, His146, Asp181, Tyr208, Tyr308, His33, Pro34	H-bonds	98-100, 104, 105
SAHA	For HDAC6 −20.231 and −10.664 For HDAC8 -4.35	HDAC4 HDAC6	His802, Asp840, His842, Gly582, His614, His610, His611, His651, Tyr782	H-bonds	101, 102
TSA	−17.547 and −11.064, -8.782	HDAC6	His610, His651, Tyr782, Pro501, Phe620, Phe680, Phe643	H-bonds, stacking	102, 106, 107
Donepezil	-19.71, -17.57, -17.567, -17.257, –15.23, -13.603, -13.2, -12.3, -12.2, -11.9, –11.5 , −10.567, -10.5, -10.46, -10.41, -10.30, -9.68, -9.17, -8.5, -8.4, -11.93*, -9.81*	AChE	Tyr122, Phe293, Arg294, Leu287, Trp284, Trp84, Ser291, Val292, Tyr335, Trp88, Trp279, Phe288, Phe290, Phe330, Tyr334, Arg289 Leu282, Phe331, Tyr121, Trp86, Glu202, Trp286, Phe295, Phe388, Tyr337, His447, Trp439, Tyr449, Val340, Gly82, Thr83, Gly121, Val132, Trp286, Tyr124, Phe338, Val294 Tyr341, Tyr72, Tyr465, Ser203, Asp74, Ser125	H-bonds, pi-alkyl bonds, pi-pi stacking, cation-pi, carbon-H-bonds, hydrophobichydrophilic	111-157
Rivastigmine	-7.64, -7.0	AChE	Tyr449, Trp439, Tyr337, Val240, Gly482, Thr83, Val132, Trp86, Gly121, Trp286, Tyr124, Tyr337, Tyr449, Val340		110, 111, 129, 137
Neostigmine	12.20 and -9.54	AChE			130
Galantamine	−10.562, -8.16, -7.1	AChE	Gly118, Gly119, Tyr121, Ala201, Glu199 Asp74, Trp86, Phe338, Tyr337 Glu202 Trp439, Gly82, Thr83, Tyr124, Gly121, Val132		133, 136, 137

*is indicated as kj/mol. Abbreviations. Xanthohumol (XN); 8-prenylnaringenin (8-PN); Acetylcholinesterase (AChE); Histone deacetylases (HDAC); Sirtuin 1 (SIRT1).

and irreversible inhibitor.[110] The binding energies of FDA-approved drugs donepezil, galantamine and rivastigmine were reported.[111] According to the recently reported studies, among the *in silico* results of FDA-approved drugs, the binding energies of donepezil were reported between -19.71 kcal/mol and -8.4 kcal/mol calculated by using various algorithms such as AutoDock Vina, Glide/SP/XP, and MOE etc.[112-128] Furthermore, docking scores were given as -10.46 kcal/mol and -7.64 kcal/mol for donepezil and rivastigmine, respectively, by using Glide/SP.[129] In our previously reported study, we calculated induced fit docking (IFD) and quantum polarized ligand docking (QPLD) scores as -12.20 kcal/mol and -9.54 kcal/mol for known inhibitor neostigmine, respectively, against AChE. In addition, it was found as -9.67 kcal/mol and -5.77 kcal/mol against BChE.[130] Recently, a flavonol glucuronide querciturone was reported for its higher docking score (-13.43 kj/mol) than the other naturally occurring compounds that had a strong binding affinity than donepezil (-9.81 kj/mol).[131] The binding energies of donepezil were reported as -11.93 kj/mol and -9.73 kj/mol for AChE and BChE, respectively.[132] In another study, the binding affinities against AChE were determined as −10.567 kcal/mol and −10.562 kcal/mol for donepezil and galantamine, respectively.[133] It was reported that the binding free energy of donepezil was -10.30 kcal/mol.[134] Whereas, the binding free energy for donepezil was given as -8.5 kcal/mol for AChE.[135] The binding energies of donepezil and galantamine were found as -10.41 kcal/mol and -8.16 kcal/mol, respectively.[136] The interactions and docking scores were reported for donepezil, galantamine and rivastigmine in detail.[137] The galantamine interactions were Asp74, Trp86, Phe338, Tyr337 and Glu202.[133] The active site residues of AChE such as Phe295, Trp86, Trp286, Tyr337, Tyr465, Tyr124, His447, Ser203 etc. with donepezil have been reported in various recently reported studies.[138-155] The interactions between the target protein and drug was reported as H bonds with Tyr122, Phe293, Arg294, alkyl bonds with Leu287, Trp284, and pi-pi stacking with Trp84, and carbon-hydrogen bond with Ser291, Val292, Tyr335.[156]

The main interactions for donepezil were reported for H bonds, hydrophobic and pi-interactions with Trp88, Trp279, Phe288, Phe290, Phe330, Tyr334, Arg289. For galantamine, the interactions with residues including Gly118, Gly119, Tyr121, Ala201, Glu199 were different than donepezil active site residues.[136] We reported in our previous study that the interactions were observed with Tyr337, Trp86, Phe338, Tyr341, Asp74, Gly120 for coumarin-based compounds.[130] In another coumarin-based study, some interactions for donepezil were mentioned as Leu282, Phe288, Phe290, and Phe331 for hydrophobic and Tyr121 for hydrophilic.[157] In one of the reported studies, donepezil had the highest score than protoberberine alkaloids against AChE and the interactions were reported.[158]

It was reported that XN inhibits Mpro and is a potent pan-inhibitor against various coronaviruses. A molecular docking approach was used to estimate the potent inhibitory activities of XN against various coronaviruses. Binding scores ranged from -6 kcal/mol to -8 kcal/mol. A hydrogen bond has been determined between XN and Cys-145 residue of SARS-CoV-2 Mpro.[65] The molecular docking study was performed against LXRα with XN. The docking scores were calculated as −7.51 and −8.64 kcal/mol for related ligands and XN, respectively. These data indicated that XN has a stronger binding affinity.[159] It was demonstrated that XN and its derivative TXN (tetrahydro-XN) could bind to the ligand binding site of PPARy (peroxisome proliferator-activated receptor gamma) with molecular docking simulations.[160] It has been estimated that XN and dapsone drugs might affect tumour progression via abnormal expression of LCAT and NAT2, respectively. For this purpose, a molecular docking study was carried out with NAT2, XN and LCAT (PDB ID 4X96). The binding score of XN was calculated as -7.1 kcal/mol. The interactions between XN and LCAT have been observed with related amino acids such as Asp56, Thr54, Lys53, and Tyr51. These results have indicated that tumour progression of high-risk COPD patients may be altered by XN and a known drug.[44] Four prenylflavonoids XN, IXN, 8-PN and a semisynthetic prenylflavonoid derivative, tetrahydroxanthohumol (TXN) were tested with *in silico* studies to understand binding potency against human farnesoid X receptor (FXR). XN binds to the ligand binding domain of FXR388. Furthermore, a molecular docking study suggests that three key functional groups in prenylflavonoids including 4-hydroxyphenyl, 2-hydroxy and carbonyl group contribute to form of H-bond with related amino acid residues of FXR-LBD.[161] Molecular docking study was performed with XN and MD2. It was reported that XN could bind to MD2 and the 4'-hydroxyphenyl of XN formed an H-bond with Arg90 at the active pocket of MD2.[162] To evaluate the binding affinity of XN, a molecular docking study was performed. XN was well localized to IKKβ. The free binding energy for XN was determined as –7.61 kcal/mol.[163] The other study focused on identifying a direct target for XN and reported that AKT kinase activity was analyzed by a molecular docking study. According to the obtained results, XN displayed H-bond interaction with Ala230, Glu228, Lys158, and Glu234 in the backbone of AKT1. In addition, the interactions with Glu236, Thr213 and Lys181 were observed for AKT2. Besides, it was indicated that XN could bind with PDK1 and p70S6K.[164] Hop-derived nine compounds against α-glucosidase were evaluated by *in silico* approaches. Molecular docking results showed that allosteric and catalytic sites of α-glucosidase interacted with IXN and lupulone, respectively. As a result of this study, it is thought that a diet rich in hops may be beneficial for hyperglycemia.[165] Prenylated flavonoids including XN, and prenylnaringenin of hops act as positive modulators of GABA-induced responses at GABA receptors. *H. lupulus* L. contains neuroactive compounds that are useful in

traditional medicine. Humulone (α-acid) and 6-PN are the most active neuroactive compounds of hops. Both humulone and 6-PN act mainly on the γ-aminobutyric acid (GABA) domain. The interactions were evaluated between humulone and other reported hop compounds active at GABA-receptors.[166] Compounds 8-PN and 6-PN were performed by molecular docking studies for type 2 diabetes-associated proteins.[76] In one of the reported studies, to investigate the binding affinities between 23 compounds including 8PN and 8-PG flavonoids and glycogen phosphorylase, MM-PBSA and MM-GBSA were calculated as (2.1 ± 0.4 kcal/mol) and (0.4 ± 0.4 kcal/mol) for 8PN, and (-4.5 ± 0.33 kcal/mol) and (-5.9 ± 0.4 kcal/mol) for 8-PG, respectively.[77] The reactions of XN, IXN, 6-PN and 8-PN with AFB1 and AFBO were investigated by *in silico* analysis with free energy calculation.[167]

In the highlight of this information, hop prenylated flavonoids could be determined by *in silico* approaches including molecular docking and simulation studies against various drug targets to identify their potential inhibitor candidate.

A Perspective of Hops Structures

Prior core structures are widely used to discover drugs in medicinal chemistry. Chalcones include α,β-unsaturated carbonyl group, and are abundantly naturally occurring compounds in plants. It is reported that these natural compounds participate in various biological activities.[168] XN has an *E*-isomer of chalcone group on the structure that increases the biological activity. These reactive carbonyl compounds are associated with broad-spectrum pharmacological properties like cancer, anti-inflammatory and immunosuppressive activities.[169] Most biologically important compounds have benzopyran (chromen) scaffolds as therapeutic agents for various diseases.[170] 8- and 6-PNs as the most known phytoestrogens include the substitution of benzopyran-4-one core structure with prenyl and free hydroxy groups. IXN contributes to higher biological activity similar to XN than 6-PN due to having a methoxy group at 5-position on the benzopyran ring. 8-PN has the strongest activity than 6-PN because of the localization of the prenyl group on the benzopyran ring. Phloroglucinol type-compounds as humulone and lupulone play a role in biological applications with their 2- and 3-prenyl groups, respectively, as well as free hydroxyl groups and the acidity of enol moiety. Figure 5 shows the structures of effective functional groups.

Conclusion

Natural products play an important role in the treatment and prevention of various human diseases. The importance of using plants as anticancer agents in modern medicine

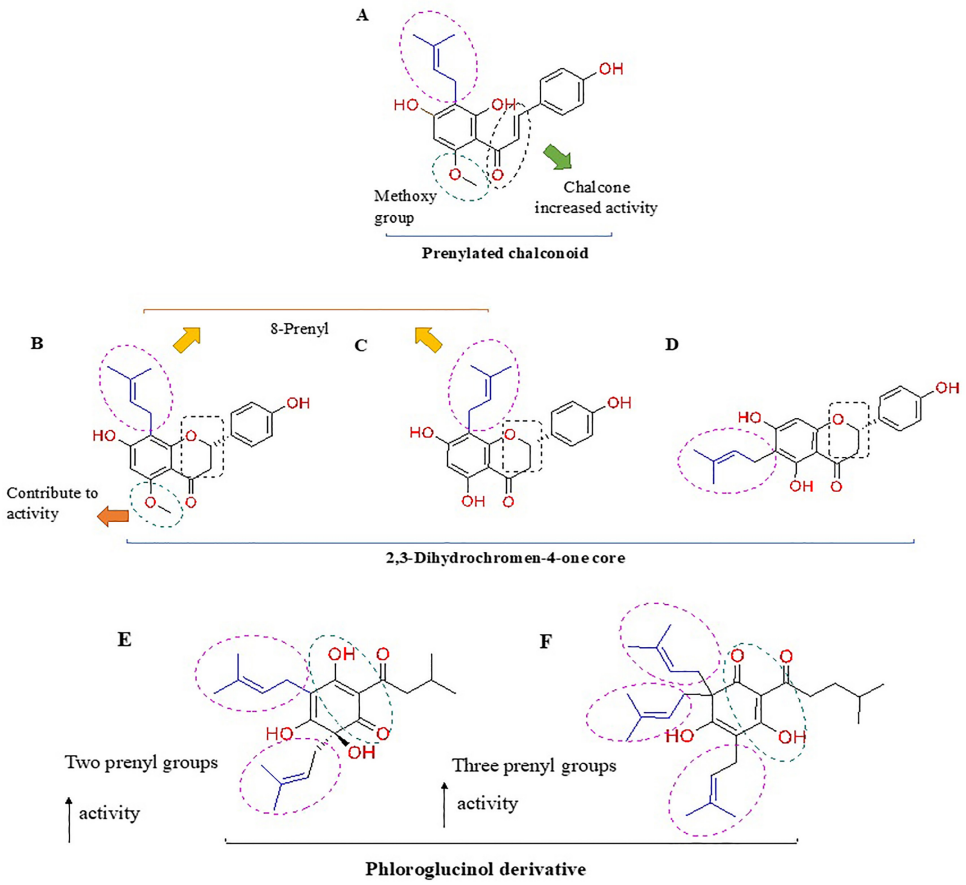

Figure 5. An overview of hops structures.

is well documented. Therefore, new sources of natural products or new structural features showing anticancer activity may contribute to the identification of promising phytotherapeutics. As a result, prenylated flavonoids including XN, IXN, 8-PN and 6-PN from hops play a role with their strong anticancer activity in many solid tumours such as glioma, breast, pancreas, prostate etc.. XN was involved in multiple signaling pathways, especially significant cancer-related pathways such as MAPK/ERK, Akt/mTOR/S6K, and was indicated as a promising candidate for further studies. miRNAs are important regulatory agents and have a role in many cancers, thus, miRNAs are promising potential targets for miRNA-targeted therapy.[171] XN regulate transcriptionally ERK/c-Fos signalling pathway by the inducing of miR-204-3p expression. It can be thought that XN or its analogues may be potential small molecule inhibitors of miRNA-targeted therapy in the future.

Recent studies showed that XN and its analogues were dramatically associated with significant drug targets such as HDACs, SIRTs, and AChE in computational analysis. We hope that hop prenylated compounds may be used for clinical translation.

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Conflict of Interest

The authors report no conflicts of interest.

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