OPEN ACCESS

Haya: The Saudi Journal of Life Sciences
Abbreviated Key Title: Haya Saudi J Life Sci
ISSN 2415-623X (Print) | ISSN 2415-6221 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

Borneol as Adjuvant Chemotherapy: A New Way for the Development of Novel Chemotherapeutic

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DOI: 10.36348/sjls.2022.v07i04.002 | **Received:** 16.03.2022 | **Accepted:** 21.04.2022 | **Published:** 25.04.2022

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Abstract

Nature has generously open life-saving remedies to mankind by offering evolutionarily optimized drug like bimolecular in the form of several natural products. These marvelous gifts of nature have been serving as most suitable candidates against the treatment of multiple disorders and particularly for cancer (2nd leading cause of death, cancer) due to their pleiotropic mode of action on target molecules. Current review intends to provide an update on the bioactivities of such gifts from nature, natural borneol, which is the major bioactive constituents of traditionally used medicines. Borneol is a monoterpenoid, isolated from different medicinal plants and have strong potential to be used against multiple disorders such as bacterial and inflammatory infections. Recently it is investigated that borneol has a great potential of inhibiting the growth of multiple neoplasms such as hepatocellular carcinoma, neuroblastoma, glioma, esophageal squamous cell carcinoma, ovarian and lung cancer. Moreover, by regulating the BBB junctions it also increases the drug concentration in cancer cells, this shows that its combine use with already practiced therapeutics may increase the efficacy of these therapeutics against cancer cells. In this review we will summarize all the studies on anticancer activity of borneol, our primary goal will be to discuss the combined use of borneol with other clinically used drugs to improve their efficacy against human cancers.

Keywords: Borneol, Chemotherapy, Adjuvant therapy, curcumin and Doxorubicin borneol.

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INTRODUCTION

The term "natural product" is usually used to refer those chemicals which are derived from nature (Nageen *et al*., 2018). The natural products contain possibly valuable bioactive agents for herbicides, pharmaceuticals, and insecticides industries. Till present time, more than 23,000 bioactive compounds have been reported since the penicillin discovery. Natural products are described as human health encouraging agents due to their high efficacy, low cost, and safety profiles (Newman *et al*., 2016). Different plants have already in use from a long time to cure numerous diseases. WHO claimed that 80% of the world population mainly depends upon plant-based medications for maintaining healthy lifestyle (Sen *et al*., 2015). Utilization of natural bioactive products have been used since 2600 BCE, when civilization of Mesopotamian used almost extract of 1000 plants to isolate various phytochemicals. Similar trend was manifested by Chinese civilization since 1100 BCE, where they used about 365 plant-based drugs (Mitin *et al*., 2016). In modern times, discovery of novel drugs from different natural sources involves the use of numerous phytochemicals, biological, molecular, and botanical techniques (Sen *et al*., 2015).

Research on different herbs and plants has been reported their high efficacy against multiple disorders. Studies have shown that bioactive molecules derived from multiple herbs and plants have antimicrobial (Hatziieremia *et al*., 2006), anticancer (Wei *et al*., 2019), anti-inflammatory (Agus Chahyadi *et al*., 2012), skin whitening agents (Lee *et al*., 2006), antioxidant (also shows that versatile pharmacological activities of medicinal plants are mainly dependent upon their phytochemical components (Amira *et al*., 2018).

Cancer is a complex disease that has been described by unrestricted proliferation of cells caused due to mutation in several important genes that involve in encoding of multiple key proteins such as anti-apoptotic, tumor suppressers proteins as well as growth factors. Cancer is the 2nd leading cause of deaths both in developed and developing countries (Ashaq *et al*., 2021). Mainly chemotherapy has been used till date for the treatment of cancer which has restricted therapeutic success due to, toxicity, high expenses, and very quick development of resistance. Moreover, chemotherapeutic agents activate multiple other signaling pathways in parallel of suppressing the growth of cancer cells, such actions of chemotherapeutic drugs also limited their efficacy against different cancer cells (Mehmood *et al*., 2017). Cancer treatment by nature-based bioactive agents is now getting fame because they can improve the limitations of the chemotherapeutic agents used today (Muller *et al*., 1973).

Most of the pharmaceutical drugs are monotarget entities but bioactive compounds are multitargeted and can control proliferation of cells and cancer growth by modifying multiple signaling pathways (Muller *et al*., 1973). It is estimated that approximately 60% of clinically used anticancer drugs have been isolated from different natural sources including microorganisms, marine biota, and plants (Dall'Acqua *et al*., 2014). Phytochemicals acquired from fruits, herbs, vegetables, and different medicinal plants have shown promising effects in reducing the burden of cancer (Rabi *et al*., 2009). Secondary metabolites such as terpenoid, phenols, polyphenols flavonoids and isoprenoids isolated from several medicinal plants have been described for their possible anticancer activities (Niedzwiecki *et al*., 2016; Akinwumi). Moreover, bioactive agents have low side effects, easily available and cost effective that's why use of biomedicines against multiple disorders has been increased day by day.

Borneol ($C_{10}H_{18}O$) is mainly obtained from a resin or dipterocarp and several medicinal plants as describes in table 1 (Gao *et al*., 2013; Xie *et al*., 2016). Borneol is a monoterpenoid and bicyclic bioactive molecule as given in figure 1. It has been widely used in drug and food industries as a valuable medicinal material and flavorant respectively (Xie *et al*., 2016). Borneol have been used as an analgesic, antibacterial, and anti-inflammatory agent (Lai *et al*., 2020). Furthermore, studies have shown that Borneol efficiently improved the availability of different less permeable therapeutics by improving permeability of cell membrane, regulating blood-brain barrier (BBB) and increasing the distribution of drugs in brain tissues (Cai *et al*., 2008; Duan *et al*., 2016). In addition to other medicinal values, it has been also reported that Borneol significantly increase the anticancer efficacy of various chemotherapeutic agents against human cancers (Su *et al*., 2016; Chen *et al*., 2014; Liu *et al*., 2018; Meng *et al*., 2018). In this review we will explore the anticancer mechanism of Borneol and discuss its multiple cellular targets in human cancers. Moreover, we will also discuss the combined use of Borneol with already used chemotherapeutics against different cancers.

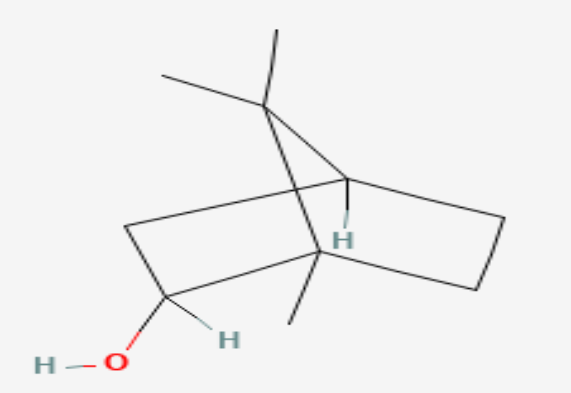

Figure 1: Molecular Structure of Borneol

Table 1: Describes different medicinal that contain borneol in their different parts.

Plants/Animal	Family	Part of the plant	References
Chrysanthemi Indicum	Asteraceae	Flowers	Deng *et al*., 2006
Amomum villosum	Zingiberaceae	Not reported	Ye *et al*., 2008
Cinnamomum camphora	Lauraceae	Leaves	Yang *et al*., 2018
Cinnamomum cassia,	Lauraceae	Leaves	Wang *et al*., 2009
Cinnamomum zeylanicum,	Lauraceae	Leaves	Wang *et al*., 2009
Cinnamomum tamala,	Lauraceae	Leaves	Wang *et al*., 2009
Cinnamomum burmannii,	Lauraceae	Leaves	Yang et al., 2020
Cinnamomum pauciflorum	Lauraceae	Leaves	Wang *et al*., 2009
Lavandula angustifolia	Lamiaceae	Leaves	Abroomand *et al*., 2011
Typus physiologions		Leaves	Zhang *et al*., 2010
Rosmarinus officinalis	Lamiaceae	Leaves	Okoh *et al*., 2010
Achillea millefolium	Asteraceae	Flowers, Leaves	Bocevska *et al*., 2007
Artemisia argyi	Asteraceae	Inflorescences	Wenqiang *et al*., 2006
Blumea balsamifera	Asteraceae	Leaves	Wang *et al*., 2014
Dryobalanops aromatica	Dipterocarpaceae	Not reported	Le *et al*., 2016
Zingiber officinale	Zingiberaceae	Rhizomes	Nishimura *et al*., 1995

Plants/Animal	Family	Part of the plant	References
Achillea monocephala	Asteraceae	Leaves, Flowers	Gogus *et al*., 2006
Artemisia annua	Asteraceae	Leaves	Quispe-Condori *et al*., 2005
Artemisia princeps	Asteraceae	Leaves	Umano *et al*., 2000
Artemisia absinthium	Asteraceae	Arial parts	Kordali *et al*., 2006
Artemisia santonicum	Asteraceae	Arial parts	Kordali *et al*., 2006
Artemisia spicigera	Asteraceae	Arial parts	Kordali *et al*., 2006
Artemisia vulgaris	Asteraceae	Not reported	Hwang *et al*., 1985
Asparagus thunbergianus	Liliaceae	Root	Rivett *et al*., 1971
Chrysanthemum morifolium	Asteraceae	Flower	Dong *et al*., 2007
Cistus ladanifer	Cistaceae	Branches	Teixeira *et al*., 2007
Fructus amomi	Zingiberaceae	Fruits	Deng *et al*., 2005 Li *et al*., 2017 Flamini *et al*., 2007
Kaempferia galanga	Zingiberaceae	Rhizome	Li *et al*., 2017
Laurus nobilis	Lauraceae	Leaves	Flamini *et al*., 2007
Micromeria cristata	Lamiaceae	Herbal parts	Tabanca *et al*., 2001
Corythucha marmorata	Tingidae	Secretions	Watanabe *et al*., 2017
Decalepis hamiltonii	Asclepiadaceae	Roots	Harish *et al*., 2005
Dendranthema nankingense	Compositae	Seeds	Kordali *et al*., 2008
Zingiber officinale	Zingiberaceae	Roots	de Melo *et al*., 2020

Anticancer effect of Borneol

In parallel to other medicinal values of borneol pile of literature showed that borneol also has a strong anticancer potential against different cancers such as hepatocellular carcinoma, neuroblastoma, glioma, esophageal squamous cell carcinoma, ovarian and lung cancer (Hur *et al*., 2013; Su *et al*., 2013; Chen *et al*., 2014; Chen *et al*., 2015b; Chen *et al*., 2015a; Zou *et al*., 2017; Liu *et al*., 2018; Meng *et al*., 2018; Chang *et al*., 2018; Lai *et al*., 2020; Yuan *et al*., 2020; Cao *et al*., 2020; Cao *et al*., 2019; Wang *et al*., 2020). Borneol reduced cell growth, increased cell cycle arrest, induced apoptosis, alleviated oxidative stress and sensitized the drug resistant cancer cells by modulating different signaling pathways such as p-Akt, p- ERK1/2 and p-JNK (Su *et al*., 2013; Hur *et al*., 2013; Chen *et al*., 2014; Chang *et al*., 2018). Main cellular targets of borneol are given in Table 2. Moreover, literature showed that there are diverse studies which explains the co treatment of borneol with different FDA approved anticancer drugs (Liu *et al*., 2018; Meng *et al*., 2018; Chang *et al*., 2018). Here in this review, we will further explain about the efficacy of borneol with different anticancer drugs and bioactive molecules against different cancers.

Table 2: Different Molecular targets of Natural Borneol in multiple cancer cell lines

Type of cancer	Cell lines	Molecular Targets		References
		Activation/Upregulation	Inhibition/Downregulation	
Hepatocellular Carcinoma	HepG2	p-Histone, p-p38, ROS, Caspase-3/8/9, Cl- PARP, Bad, Bax, t- Bid, p-p53,	p-Akt, p- ERK1/2, Bcl-XL, Bcl-2, Mcl-1	(Su *et al*., 2013)
		p-ATM, G2/M arrest, p-p53, p21, p-Histone	Cdc2, cyclin B, p- MDM2, ABCB1,	(Chen *et al*., 2015)
		TMEM65, FTH1, CTSB, Ca5b, PPP6C, BCKDHB, MRPL39, HNRNPU, Fdps, AHCY, Fam185a, PDHA1, RCN3, RCN3, P4HA1, NDUFS1, ALDH1L2, G2/M arrest, p21, p-p53, p-ATM, ROS	APOA1, PSMA5, PRSS1, CAPZA1, DDX56, PDIA3, Pdia3, HNRNPU, FHL3, NPM, HNRNPC, HSPA9, Cyclin B1, Cdc2, MDM2, ABCB1,	(Chen *et al*., 2015a)
		Ub-YFP, pre-G1 & G0/G1 arrest, p62	20S, 26S, USP47	(Chang *et al*., 2018)
Neuroblastoma	SH-SY5Y	HO-1, Nrf2, Bcl-2,	ROS, Bax,	(Hur *et al*., 2013)

Melanoma	A375	sub-G1 arrest, Cl-PARP, p- JNK, ROS, p-ATM, p- Brca1, p-p53, Caspase-3/8/9,	p-ERK, Akt	(Chen *et al*., 2014)
Glioma	U251	Caspase-3/8/9, p-ATM, ATR, p- p53, ROS, p-JNK, p-P38, p-ERK, Sub G1 arrest, p-Histone,	Akt	(Cao *et al*., 2020)
	U87	ROS, p-ATM, p-ATR, p-p53, G2/M arrest, p- histone, p21, p-P38,p-ERK,	Cyclin B, Cdc2, Akt Ki-67, CD34	(Cao *et al*., 2019)
	U251	Caspase-3/8/9, Bax, Bad, ROS, p-ATM, p-ATR, p-p53, p-histone H2A.X, p21	MMP, Bcl-2, Bcl-XL	(Liu *et al*., 2018)
	U251	Caspase-3, Bax,	HIF-1 α, mTORC1, eIF4E, Bcl-2, p-eif4e	(Wang *et al*., 2020)
Esophageal Squamous cell Carcinoma	TE-1 TE-13,	Caspase-3,	survivin , P-AKT	(Meng *et al*., 2018)
Ovarian Cancer	A2780 paclitaxel resistant A2780/PTX		P-gp, MMP	(Zou *et al*., 2017)
Lung Cancer	A549	p- JNK, ROS, p-p53, TRPM8, Caspase-3/8/9, Cl- PARP, t-Bid, Bax, p-ATM, p-ATR, p- histone H2A.X,	p-ERK, p-Akt, MMP, Bcl-2	(Lai *et al*., 2020)
		Sub G1, ROS, FADD, RIPK1	EHD1	(Yuan *et al*., 2020)

Borneol as an Adjuvant Therapy

Mostly drugs used for cancer treatment are highly specific in their targets, but as cancer is caused by multiple mutations (Ashaq *et al*., 2021), thus it is usually observed that the cotreatment of more than one drugs in the treatment of cancer is more effective as compared to monotherapy. Recently it is reported that borneol (BRN) works along with different chemotherapeutic agents to boost the antineoplastic effect by different mechanisms (Chen *et al*., 2015; Cao *et al*., 2020; Cao *et al*., 2019). It is reported that BRN enhanced the anticancer effect of different clinically used anticancer drugs and bioactive molecules such as doxorubicin (DOX), curcumin (Cur), cisplatin and paclitaxel (Ptx) (as in table 3) by increasing the production of reactive oxygen species (ROS) that may induce cell cycle arrest, DNA damage (Cao *et al*., 2019) and activate p53 pathway (Chen *et al*., 2015), and enhancing apoptotic rate by regulating the expressions of multiple proapoptotic MAPK proteins and PI3K/Akt pathway in U251 cells (Cao *et al*., 2020; Yuan *et al*., 2020).

In addition to all this, BRN has been reported to easily cross the blood-brain barrier (BBBr), and some anticancer drugs, such as nimustine, arsenic trioxide, cisplatin, and methotrexate promoted its penetration through the BBBr (Xiao *et al*., 2009; Guo *et al*., 2008; Wang *et al*., 2020). Effect of cotreatment of BRN with different anticancer drugs and bioactive molecules is given in table 2. Further we will describe the cotreatment of BRN with different clinically practiced drugs and plant derived bioactive molecules.

Table 3: Action of combined use of Natural Borneol with different therapeutics

Cancer Type (Cell lines)	Natural Borneol (Concentration)	Drug (Concentration)	Mode of Action	Reference
Human Melanoma (A375)	40 mg/ml	Cur (10-40 µM)	Natural broneol (NB) synergized the anticancer potential of Curcumin (Cur) in A375 cells	(Chen *et al*., 2014)
Human Glioma (U251 and U87)	(80 µg/ml)	Doxorubicin (DOX) (0.4 -0.8 µM)	NB synergized DOX-induced antineoplastic efficiency in glioma cells by increasing the uptake of DOX.	(Cao *et al*., 2019)
Human Glioma (U251 and U87)	NB (5–80 µg/ml)	Cisplatin (40 µg/ml)	NB synergistically increased cisplatin-induced cell death in human glioma.	(Cao *et al*., 2020)
Hepatocellu-lar Carcinoma (HepG2)	NB (20 µg/ ml)	BDCur (40 µM)	NB enhanced the antiproliferative effect of BDCur by increasing uptake of BDCur via downregulation of ABCB1 expression.	(Chen *et al*., 2015 a)
Hepatocellu-lar Carcinoma (HepG2)	NB (20 µg/ml)	Cur (20 µM)	NB boosted the anticancer effect of Cur by increasing the cellular concentration of Cur through downregulating the expression of ABCB1.	(Chen *et al*., 2015 b)
Glioma (HBMEC, C6)	NB (10 µg/mL)	Angiopep-2-modified, DOX-loaded PAMAM Dendrimer (20 µM/L)	NB synergized the antiglioma activity of DOX-loaded dendrimers by boosting its BBB penetration.	(Han *et al*., 2017)
Lung Cancer (A549)	NB (40-160µg/mL)	DOX (.25 µM)	NB enhanced the antcancer activity of Doxorubicin through synergistic effects in A549 lung cancer cells	(Lai *et al.*, 2020)
Human Glioma (U251)	NB (80 µM)	Temozolomide (TMZ) (40 µM)	NB enhances TMZ-mediated antineoplastic efficiency against U251 through enhancing mitochondrial dysfunction and ROS-mediated DNA damage	(Liu *et al*., 2018)
Human Glioma (C6, BMEC cells)		DOX BO-PMs	Increased cytotoxicity of Dox by increasing its transport efficiency across BBB and quick accumulation in brain tissues.	(Meng *et al*., 2019)
Esophageal squamous cell carcinoma (TE-1, TE-13)	NB (20-80 µg/mL)	Paclitaxel (PTX) (15 µM)	NB synergistically enhances the anticancer activity of Paclitaxel by increasing cellular accumulation of Paclitaxel in ESCC cells.	(Meng *et al*., 2018)
Hepatocellu-lar carcinoma (HepG2)	NB (80 & 160 µg/mL)	Selenocystine (20 & 40 µM)	NB effectively synergizes the Selenocystine-mediated cell death by enhancing cellular uptake of Selenocystine and activation of ROS-mediated DNA damage.	(Su *et al*., 2013)
Glioma (C6)		BOR/PTX LANs (BOR: 1.0 µg/ml and PTX LANs: 50 µg/ml)	NB in the form of BOR/PTX LANs sensitizes the PTX resistant cells by increasing its cellular uptake and accumulation of PTX inside the tumor tissue via inhibition of p-gp protein.	(Tang *et al*., 2015)
Glioblastoma (U87MG)	NB (10 µg/ml)	CGKRK-PSNPs (200 µl)	NB enhances the cytotoxicity of CGKRK-PSNPs in U87-MG cells by increasing its transportation across BBB.	(Lv *et al*., 2020)
Lung cancer (A549)	NBNPs (160-400 µM)	Gefitinib (20-40 µM)	NBNPs synergistically potentiate the anticancer effect of Gefitinib by increasing cellular concentration of Gefitinib.	(Yuan *et al*., 2020)
Ovarian cancer (A2780/PTX cells)		PTX+NB co-delivery PEG-PAMAM NPs	NB synergized the anticancer activity of PTX by increasing the cellular concentration of PTX in ovarian cells, via downregulation of p-gp protein.	(Zou *et al*., 2017)

Doxorubicin and Borneol

DOX, an anthracenedione easily soluble in water, is the most efficient and broadly practiced chemotherapeutic mediator, which shows a wide range of cytotoxicity against different tumors (Chlebowski *et al*., 1979). Recently it has become a clear crystal fact

that, DOX has severe harmful effects, such as dose-limiting myelosuppression and lethal cardiotoxicity (Carvalho *et al*., 2009). Moreover, the antineoplastic activity of DOX can be reduced by the MDR that is carried out by multiple drug efflux pumps (Wijdeven *et al*., 2016; Lipinska *et al*., 2017). Hence, lessening adverse effects, conquering chemo-resistance, and augmenting the antiproliferative activity remained the major hurdle for DOX-based treatment.

Now days, adjuvant therapy has become a promising method of searching novel chemo-sensitizers (Zhong *et al*., 2018; Cao *et al*., 2019). NB is a naturally occurring monoterpenoid which has been reported as a potential chemosensitizer. It is reported that NB has a strong potential to increase the cytotoxicity of DOX against different neoplasms by increasing cellular uptake and drug accumulation of DOX (Han *et al*., 2017; Cao *et al*., 2019; Meng *et al*., 2019). Meng *et al*., (2019) reported that natural borneol-modified nanomicelles loading doxorubicin (DOX BO-PMs) effectively increased the cellular uptake of DOX in the C6 and HBMEC cells through BBB by opening the tight intracellular junctions in the BBB, changing its conformation, enhancing the interactions of cell membrane, and accelerating the transport of nanomicelles.

Increase in cellular accumulation of DOX by NB also increases the anticancer effect of DOX in C6 via inhibition of cell growth in C6 cells. Moreover, it's quite surprising that NB specifically acted on BBB not on tumor cells. In addition to increase the cellular accumulation of DOX, DOX BO-PMs also increased the antimetastatic activity of DOX in liver cells and glioblastoma mouse model (Meng *et al*., 2019). Therefore, Angiopep-2 can be used for drug delivery into the brain and the glioma cells (Ji *et al*., 2019). Researcher shows that angiopep-2-PEG-PAMAM/DOX dendrimers modified with NB increased the anti-glioma activity of DOX by boosting BBB penetration of DOX-loaded dendrimers in C6 and HBMEC cells (Han *et al*., 2017). Another study conducted by Cao *et al*., (2019) demonstrated that NB enhanced the cellular uptake of DOX by increasing its BBB permeability (from 23.5% to 57.6%) in U251 cells. NB (20–160 μg/ml) alone did not reduce the cell growth in U251 cells but combined treatment of NB (80 μg/ml) with 0.4 or 0.8 μM DOX significantly increased the DOX-mediated growth inhibition of U251 cells. In addition, the decline of cell populations, cell shrinkage and cell rounding are also confirmed this conclusion.

Furthermore, NB also increased the growth inhibitory action of DOX by arresting cell cycle at G2/M phase via downregulation of Cyclin B1 and cdc2 (Cao *et al*., 2019). In A549 cells alone DOX (0.06 μM to 0.25 μM) showed a slight growth inhibitory effect but strong growth inhibition was observed in A549 cells pretreated with NB chased by low dose of DOX, with suppression ratio enhanced up to 40.26%. In A549 cells NB mainly increase the cytotoxic activity of DOX by increasing its cellular uptake and inhibiting the activity of P-glycoprotein (P-gp: one 9 of the major causes of DOX-resistance). NB boosted the DOX-induced cell death in A549 cells by increasing DOX-mediated apoptosis. NB enhanced the DOX-mediated activation of caspases cascade and increased apoptosis by upregulating both intrinsic and extrinsic apoptosis followed by PARP cleavage in A549 cells. Lai *et al*., (2020) also confirmed that NB and DOX have no cytotoxic effect on normal NCM-460 cells (colonic cells) which further confirmed the effective combined use of NB and DOX for cancer cells (Lai *et al*., 2020).

ROS plays crucial role in regulating cell proliferation, growth, migration, and death. Overproduction of ROS may cause DNA damage and regulate DNA damage-mediated different signaling transduction. NB increased the DOX-induced production of ROS, that ultimately augmented the DOX-mediated DNA damage as also evidenced by increased activation of phosphorylated ATR, p53, ATM, total p21 and histone H2A.X in U87 and A549 cells (Cao *et al*., 2019; Lai *et al*., 2020). Pretreatment of U87 cells with 5mM GSH significantly reduced the NB-DOX-induced DNA damage as reported by weak phosphorylation of ATR, p53, ATM, total p21, histone H2A.X and retrieved expressions of Cyclin B in U87 cells. These results disclosed that ROS as an influential upstream regulator aided to cotreatment-induced antineoplastic efficiency against glioma growth (Cao *et al*., 2019). In addition to it, Lai *et al*., (2020) demonstrated that DNA damage-mediated activation of p53 also contributed to the sensitizing impacts of NB on DOX in A549 cells. In A549 cells NB also synergistically enhanced the killing potential of DOX by increasing the mitochondrial dysfunction that was evidenced by lower membrane potential ($\Delta\psi m$), increase expression of Bax and tBid and decrease expression of Bcl-2 (Lai *et al*., 2020).

PI3 K/AKT and MAPKs pathways have significant role in cell proliferation, survival, and death via phosphorylation of multiple substrates, thus inhibition of these pathways may reduce cell proliferation of different neoplasms. NB in cotreatment with DOX significantly cause the dysfunction of PI3 K/AKT and MAPKs pathways by dephosphorylating AKT (Ser473) and phosphorylating the ERK (Thr202) and p38 (Thr180) in U87 cells. Moreover, pretreatment of U87 cells with MAPKs and PI3K/AKT inhibitors may reduce the growth inhibitory effect of NB-DOX (Cao *et al*., 2019). In another study Lai *et al*., (2020) also reported that, in A549 cells NB synergize the DOX-induced apoptosis by inhibiting ERK and AKT activation while increasing the JNK and p38MAPK activation (Lai *et al*., 2020).

Besides *in vitro* studies NB also augmented DOX-mediated antineoplastic efficacy *in vivo*. Cao *et al*., (2019) showed that caudal vein administration of NB+DOX (20-40mg/kg NB+ 2mg.kg DOX) synergistically increased the anticancer effect of DOX in U251 cells bearing nude mice without significant loss of body weight in nude mice. Results of this in vivo study also showed that combined use of NB and DOX also arrested the cell cycle at G2/M phase and in vivo DNA damage as evidenced by phosphorylation of histone and inhibition of Cyclin B respectively. In addition to this immunohistochemical staining has demonstrated that combined treatment also eradicated expressions of CD34 and Ki-67, which are the key markers of angiogenesis and phosphorylation (Cao *et al*., 2019).

In another in vivo study NB+DOX have been administered both orally and intravenously in A549 cells bearing nude mice. Results of this study indicated that combined use of NB+DOX significantly reduced the tumor volume after 15 days of treatment in both orally and intravenously animal model but results clearly demonstrated that intravenously administration of NB+DOX showed more effective antitumor effect than oral administration. In addition, to all this concentration of DOX in tumor tissues was also high among intravenously administered group. Moreover, decreased expressions of Ki-67 and CD34 were also observed in tumor sections. Furthermore, in A559 cells NB synergize with DOX to accomplish potent anticancer efficacy through prompting intracellular Ca2+ mobilization by intermingling with TRPM8 (Lai *et al*., 2020).

Selenocystine and Borneol

Selenium (Se) has been found as an essential (trace) element of fundamental importance for both animals and humans. It has become a clear crystal fact that specific amount of Se can inhibit the growth of many neoplasms particularly in colon, lung, prostate, and liver cancers (Chen *et al*., 2009; Rayman *et al*., 2005). Studies have also inferred that Se can be clinically used in chemotherapeutic strategies (Bjorkhem-Bergman *et al*., 2005; Fan *et al.*, 2009). However, Se presented a narrow margin between the toxic and beneficial effects. The effective concentration of Se as an antineoplastic agent, is too close to its toxic range, which significantly reduced its clinical application. Moreover, being a trace element, it may cause severe toxicity in normal cells when it's taken in excess amount. Many studies have been clearly revealed that the toxic and beneficial effects of Se on human body were strongly corelated to its chemical forms and concentration (Rayman *et al*., 2005; Bjorkhem-Bergman *et al*., 2005; Fan *et al*., 2009). Selenocystine (SeC), a diselenide oxidative product of selenocysteine, has been reported to minimize the tobacco-derived nitrosamine-induced lung cancer in A/J mice (Li *et al*., 2007).

Moreover, SeC induced apoptosis in cancer cells by increasing the production of ROS (Chen *et al*., 2009), which subsequently increased the DNA damage-mediated expressions of p-p53 and lowered the expressions of ERK and Akt. Besides *in vitro* studies SeC also possessed *in vivo* anticancer actions by increasing the apoptosis in animal model (Chen *et al*., 2008). However, the low solubility of SeC and poor stability hampered its permeabilization across cell membrane and further development as an antitumor drug (Su *et al*., 2013). Therefore, its hypothesized that cotreatment of SeC with other biologically active molecules may increase its anticancer potential against various neoplasms. Su *et al.,* (2013) suggested that NB can enhance the in vitro anticancer activity of SeC by increasing its cellular concentration in cancer cells. Results of Su *et al*., (2013) showed that pretreatment of HepG2 cells with NB (80 mg/mL and 160 mg/mL) significantly increased cellular uptake of SeC from 0.07 mg/107 cells (control) to 2.56 mg/107 cells, which was 1.6 times higher as compared to SeC alone. In addition, cotreatment of SeC (20 mM) and NB (80 mg/mL) noticeably increased the growth inhibition in HepG2 cells by inducing apoptosis which was evidenced by increased nuclear condensation, DNA fragmentation and increased expressions of caspase-3/8/9, caspase-3/7, and cleaved PARP in HepG2 cells. Furthermore, results of western blot described that cotreatment of HepG2 cells with SeC and NB increased the expressions of Bad, Bax, truncated Bid (tBid) and decreased expressions of Bcl-2, Bcl-XL and Mcl-1 (Su *et al*., 2013). tBid an activated form of Bid protein and member of BH3 domain-protein family, is well known due to its proapoptotic activity and build a link between the intrinsic and extrinsic apoptotic pathways. Moreover, activation of tBid causes its translocation from cytoplasm to mitochondrial membrane and led to oligomerization Bax and Bak, thereby increase the release of proteins from mitochondria to cytoplasm.

Synergistic apoptotic effect of SeC and NB in HepG2 cells was further evidenced by increased expressions of p- p38 MAPK and decreased expressions of p-ERK1/2 and p-Akt. Su *et al.*, (2013) also suggested that SeC and NB potentially increased ROS production in HepG2 cells, surprisingly pretreatment of HepG2 cells with NAC significantly reduced the SeC and NB induced apoptosis in HepG2 cells, these results clearly concluded that ROS may act as upstream regulator SeC and NB induced apoptosis (Su *et al*., 2013).

Curcumin and Borneol

Curcumin (Cur), bis(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene- 3,5-dione, is a biologically active constituent of *Curcuma longa*, which is extensively used in food industry as a coloring agent, spice, food preservative as well as major component of various traditional medicines. In last few years, pile of studies clearly reported that Cur can be potentially used as an antioxidant, antiproliferative, anti-inflammatory,

antiangiogenic, and anticancer agent. Different studies reported that Cur can inhibit the growth of multiple neoplasms such as hepatocellular carcinoma, thyroid cancer, colon cancer, breast cancer, bladder cancer, and ovarian cancer. Despite of its wide range bioactivities, its application is very limited because of its poor absorption, low bioavailability, and rapid metabolism. Several methods such as preparation of liposomes, nanoparticles, phospholipid complexes, micelles, and structural analogues of Cur have been used to enhance its cellular uptake and absorption rate. In addition to all this, recently it is proposed that combination of Cur with different drugs can also be used to increase the bioavailability of Cur which may increase its medicinal value. In recent decades it is reported that anticancer potential of Cur can be easily enhanced by its cotreatment with NB (Chen *et al*., 2014; Chen *et al*., 2015b).

Results of different studies have been reported that NB noticeably increased the cellular concentration of Cur in time-dependent manner, thus, pretreatment of A375 and HepG2 cells with NB (20-40 mg/ml) significantly decreased the cell viability in Cur-treated A375 and HepG2 from 70% to 54.20% (Chen *et al*., 2014; Chen *et al*., 2015b). Combined use of NB and Cur can potentially induce apoptosis in cancer cells by regulating different pathways. Chen *et al*., (2014) revealed that combined use of Cur and NB induced a significant nuclear condensation and DNA fragmentation in A375 cells which were not found in the cells treated with Cur and NB alone. Literature showed that cotreatment of Cur and NB noticeably augmented the activation of caspase-3/8/9 which ultimately increased the expressions of cleaved PARP in A375 cells. Activation of caspase-3/8/9 in A375 cells on the cotreatment of Cur and NB clearly demonstrated that both Cur and NB can induce apoptosis in cancer cells by activating both intrinsic as well as extrinsic apoptotic pathways.

Pretreatment of A375 cells followed by Cur treatment significantly increased the production of ROS which resulted in the increased phosphorylation of p-p53, p-ATM, p-Brca1 and p-JNK while decreased the expressions of p-AKT and ERK1/2 in a dose-dependent manner (Chen *et al*., 2014). Studies also have suggested that the mitogen-activated protein kinases (MAPKs) signaling pathway plays a vital role in the action of different chemotherapeutic treatments (Chen *et al*., 2008) and regulating progression of cell cycle and cell death or growth. Jun amino terminal kinases (JNK), extracellular regulated protein kinases (ERK) and p38MAPK pathways are the three most valuable pathways in MAPKs pathway. p38MAPK and JNK are mostly activated by stress and enhanced apoptosis, whereas ERK, could avert cell apoptosis by redcucing the activation of caspases (Bold *et al*., 2002). The Akt pathway also played a crucial role in cell proliferation and cell death by transferring different signals to inhibit apoptosis (Abrams *et al*., 2010; Cho *et al*., 2013).

Above discussed results clearly demonstrated that Cur/NB caused the upregulation of ROS, that plays a major role in the activation and inhibition of JNK and AKT and ERK respectively to increase the Cur/NB induced cytotoxicity and apoptosis in A375 cells. Different studies revealed that proteasome subunit alpha type-5 (PSMA5), nucleophosmin (NPM) and heterogeneouscnuclear ribonucleoproteins C1/C2 (hnRNPC1/C2) proteins involved in DNA repair, RNA splicing, apoptosis, and cell cycle arrest (Chen *et al*., 2015 b). PSMA5 is a subunit of 20S proteasome, a proteolytic enzyme found in the nucleus and cytoplasm of eukaryotic cells (Han *et al*., 2004). Previous studies reported that inhibition of the PSMA5 can cause cell cycle arrest and apoptosis in cancer cells (Xu *et al*., 2008; Liu *et al*., 2004; Clarke, 2002). hnRNP C1/C2, a member of hnRNP family, is a nuclear pre-mRNA binding factor that mainly regulate processing of pre-mRNA, apoptosis, and cell cycle. NPM is a vital player in regulation of cell cycle, response of DNA-damage and an important modulator of p53 by regulating the expressions of Mdm2 (Chen *et al*., 2015b). In a recent research it is documented that NB/Cur can induce cell cycle arrest by modulating PSMA5, NPM and hnRNP C1/C2 which ultimately leads to apoptosis in cancer cells. Results of a recent report demonstrated that NB/Cur exposure to HepG2 cells markedly induced cell cycle arrest at G2/M phase by upregulating the expressions of p21, p-p53, p-ATM, ROS and downregulating the expressions of cyclin B1, cdc2, PSMA5, NPM, Mdm2 and hnRNP C1/C2 (Chen *et al*., 2015b). Interestingly, pretreatment of HepG2 cells with NAC significantly reduced the NB/Cur-induced G2/M phase arrest from 33.1% (when exposed only to NB/Cur) to 13.9% (when pretreated with NAC), which was evidenced by downregulation of p21, p-p53, and p-histone. These results clearly depicted that ROS can be an upstream target of G2/M phase arrest in HepG2 cells, thus plays a crucial role in NB/Cur-induced apoptosis in HepG2 cells (Chan *et al*., 2015b).

Bisdemethoxycurcumin (BDCur) and Natural Borneol

Turmeric's major constituents include curcumin (Cur), bisdemethoxycurcumin (BDCur) and demethoxycurcumin (DCur). Many studies have been suggested the beneficial impacts of curcuminoids, particularly Cur. Studies have been proven that Cur possesses anti-inflammatory, antioxidant, anticancer and anti-angiogenic activities (Yang *et al*., 2012; Shi *et al*., 2006). In parallel to Cur, only a few studies have been reported about the beneficial effects of BDCur, a dimethoxy derivative of Cur (Chen *et al*., 2015a). Recent studies have suggested that BDCur inhibited the cell proliferation and survival of different neoplasms including breast cancer, colon cancer, leukemia, and glioma cells. In addition, BDCur suppressed cancer

invasion and metastasis by suppressing MMPs and uPA in HT1080 cells (Chen *et al*., 2015 a; Ramezani *et al*., 2017). However, its beneficial effects are extremely limited due to its low absorption which might be due to its poor water solubility. Therefore, anticancer activities of BDCur can be enhanced by increasing its cellular uptake. Recently Chen *et al*., (2015) has been reported that antineoplastic action of BDCur can be increased by its cotreatment with NB. Results of MTT assay showed that BDCur (10, 20, 40, 80 μM) alone can induce cytotoxicity in HepG2 cells and L02 cells in a dose-dependent manner, but cell viability was quite high in L02 cells as compared to HepG2 cells. NB (10, 20, 40, 80 μg/ml) alone did not inhibit the cell growth in HepG2 and L02 cells. Further studies suggested that NB increased the anticancer potential of BDCur by increasing its cellular concentration in HepG2 cells in a time-dependent manner via inhibition of ABCB1 (Chen *et al*., 2015 a). Growth inhibitory mechanism of BDCur and NB suggested that combined use of both BDCur and NB significantly induced cell cycle arrest in HepG2 cells at G2/M phase, which is evidenced by high level of ROS, increased expression of p21, p-p53, p-ATM, p-histone (Ser 139 site) and decreased expression of p-MDM2, Cdc2 and Cyclin B1 in HepG2 cells. Chen *et al*., (2015 a) also described that pretreatment of HepG2 cells with NAC (inhibitor of ROS generation) significantly reduced the growth inhibitory effect of NB/BDCur which clearly shows the ROS as upstream target of cell cycle arrest in HepG2 cells (Chen *et al*., 2015a).

CONCLUSION

Borneol is a bioactive molecule that belongs to terpenoid, a group of secondary metabolites of plants. It has been reported that borneol has wide medicinal value to be used against different disorders. In our review we clearly discussed about the anticancer effect of borneol, borneol has potential to reduce the growth of multiple neoplasms by regulating different signaling pathways. It induces apoptosis in different cancer cells by increasing the expressions of proapoptotic proteins, lowering the antiapoptotic proteins and activating both intrinsic and extrinsic pathways of apoptosis. It also suppressed the cell growth by modulating different pathways including MAPKs and PI3k/Akt pathway. Moreover in vivo studies shows that it has very high cytotoxicity for cancer cells while very low toxic effect for normal cells. In combined use with other clinically used drugs borneol significantly increased their concentration in cancer cells and thus improve their efficacy against cancer cells in vitro. In addition to all this borneol also sensitize the drug resistance cancer cells by inhibiting the expressions of p-gp. All these studies clearly describe the potential role of borneol against different neoplasms, however further preclinical and clinical trials are needed to ensure its development as a novel therapeutic for cancer.

REFERENCES

- Abrams, S. L., Steelman, L. S., Shelton, J. G., Wong, E. W., Chappell, W. H., Bäsecke, J., ... & McCubrey, J. A. (2010). The Raf/MEK/ERK pathway can govern drug resistance, apoptosis and sensitivity to targeted therapy. *Cell cycle*, *9*(9), 1781-1791.
- Abroomand, A. P., Torabbeigi, M., Sharifan, A., & Tehrani, M. S. (2011). Chemical composition and antibacterial activity of the essential oil of Lavandula angustifolia isolated by solvent free microwave assisted extraction and hydrodistillation.
- Aderogba, M. A., Kgatle, D. T., McGaw, L. J., & Eloff, J. N. (2012). Isolation of antioxidant constituents from Combretum apiculatum subsp. apiculatum. *South African Journal of Botany*, *79*, 125-131.
- Chahyadi, A., Hartati, R., & Wirasutisna, K. R. (2014). Boesenbergia pandurata Roxb., an Indonesian medicinal plant: Phytochemistry, biological activity, plant biotechnology. *Procedia Chemistry*, *13*, 13-37.
- Akinwumi, B. C., Bordun, K. A. M., & Anderson, H. D. (2018). Biological activities of stilbenoids. *International journal of molecular sciences*, *19*(3), 792.
- Amira, A., El-Anssary, Rehab A. Hussein, (2018) Plants secondary metabolites: the key drivers of the pharmacological actions of medicinal plants, Herbal Medicine, Philip F. Builders, IntechOpen, https://doi.org/10.5772/intechopen. 76139.
- Ashaq, A., Maqbool, M. F., Maryam, A., Khan, M., Shakir, H. A., Irfan, M., ... & Ma, T. (2021). Hispidulin: A novel natural compound with therapeutic potential against human cancers. *Phytotherapy Research*, *35*(2), 771-789.
- Bjorkhem-Bergman, L., Torndal, U. B., Eken, S., Nystrom, C., Capitanio, A. (2005) Selenium prevents tumor development in a rat model for chemical carcinogenesis. *Carcinogenesis* 26, 125–131.
- Bocevska, M., & Sovová, H. (2007). Supercritical CO2 extraction of essential oil from yarrow. *The Journal of supercritical fluids*, *40*(3), 360-367.
- Boldt, S., Weidleand, U.H., Kolch, W. (2002). The role of MAPK pathways in the action of chemotherapeutic drugs. *Carcinogenesis* 23: 1831–1838.
- Cai Z., S. Hou, Y. Li, B. Zhao, Z. Yang, S. Xu, J. Pu (2008) Effect of borneol on the distribution of gastrodin to the brain in mice via oral administration. *J. Drug Target.* 16 (2) , 178-184
- Cao, W. Q., Li, Y., Hou, Y. J., Yang, M. X., Fu, X. Q., Zhao, B. S., ... & Fu, X. Y. (2019). Enhanced anticancer efficiency of doxorubicin against human glioma by natural borneol through triggering ROS-

mediated signal. *Biomedicine & Pharmacotherapy*, *118*, 109261.

- Cao, W. Q., Zhai, X. Q., Ma, J. W., Fu, X. Q., Zhao, B. S., Zhang, P., & Fu, X. Y. (2020). Natural borneol sensitizes human glioma cells to cisplatin-induced apoptosis by triggering ROS-mediated oxidative damage and regulation of MAPKs and PI3K/AKT pathway. *Pharmaceutical biology*, *58*(1), 72-79.
- Cao, W. Q., Zhai, X. Q., Ma, J. W., Fu, X. Q., Zhao, B. S., Zhang, P., & Fu, X. Y. (2020). Natural borneol sensitizes human glioma cells to cisplatin-induced apoptosis by triggering ROS-mediated oxidative damage and regulation of MAPKs and PI3K/AKT pathway. Pharmaceutical biology, 58(1), 72-79.
- Cao, W.-q.; Li, Y.; Hou, Y.-j.; Yang, M.-x.; Fu, X.-q.; Zhao, B.-s.; Jiang, H.-m.; Fu, X.-y. Enhanced Anticancer Efficiency of Doxorubicin against Human Glioma by Natural Borneol through Triggering ROSMediated Signal. Biomed. Pharmacother. 2019, 118, 109261.
- Carvalho, C., Santos, R. X., Cardoso, S., Correia, S., Oliveira, P. J., Santos, M. S., & Moreira, P. I. (2009). Doxorubicin: the good, the bad and the ugly effect. *Current medicinal chemistry*, *16*(25), 3267-3285.
- Chang, T. L., Liou, P. S., Cheng, P. Y., Chang, H. N., & Tsai, P. J. (2018). Borneol and Luteolin from Chrysanthemum morifolium regulate ubiquitin signal degradation. *Journal of agricultural and food chemistry*, *66*(31), 8280-8290.
- Chen, J., L. Li, J. Su, B. Li, T. Chen, Y.S. (2014). Wong Synergistic apoptosis-inducing effects on A375 human melanoma cells of natural borneol and curcumin PLoS One, 9 (6), Article e101277
- Chen TF, Wong YS (2008) Selenocystine Induces S-Phase Arrest and Apoptosis in Human Breast Adenocarcinoma MCF-7 Cells by Modulating ERK and Akt Phosphorylation. *J Agr Food Chem*, 56, 10574–10581.
- Chen, T.F., Wong, YS. (2009) Selenocystine induces reactive oxygen speciesmediated apoptosis in human cancer cells. *Biomed Pharmacother*, 63, 105–113.
- Chen, J., Li, L., Su, J., & Chen, T. (2015 a). Natural borneol enhances bisdemethoxycurcumin-induced cell cycle arrest in the G2/M phase through up-regulation of intracellular ROS in HepG2 cells. *Food & function*, *6*(3), 740-748.
- Chen, J., Li, L., Su, J., Li, B., Chen, T., & Wong, Y. S. (2014). Synergistic apoptosis-inducing effects on A375 human melanoma cells of natural borneol and curcumin. *PLoS One*, *9*(6), e101277.
- Chen, J., Li, L., Su, J., Li, B., Zhang, X., & Chen, T. (2015 b). Proteomic analysis of G2/M arrest triggered by natural borneol/curcumin in HepG2 cells, the importance of the reactive oxygen species-p53 pathway. *Journal of agricultural and food chemistry*, *63*(28), 6440-6449.
- Chen, T., & Wong, Y. S. (2009). Selenocystine induces reactive oxygen species–mediated apoptosis in human cancer cells. *Biomedicine & Pharmacotherapy*, *63*(2), 105-113.
- Chlebowski, R. T. (1979). Adriamycin (doxorubicin) cardiotoxicity: a review. *Western Journal of Medicine*, *131*(5), 364.
- Cho, H.J., Suh, D.S., Moon, S.H., Song, Y.J., Yoon, M.S., et al. (2013) Silibinin inhibits tumor growth through downregulation of extracellular signal-regulated kinase and akt in vitro and in vivo in human ovarian cancer cells. J Agric Food Chem 61: 4089–4096.
- Clarke, D.J. (2002) Proteolysis and the cell cycle. *Cell Cycle*. 1, 233-234.
- Dall'Acqua, S. (2014) Natural products as antimitotic agents. Curr Top Med Chem. 14, 2272-85.
- Danh, L. T., Triet, N. D. A., Zhao, J., Mammucari, R., & Foster, N. (2013). Comparison of chemical composition, antioxidant and antimicrobial activity of lavender (Lavandula angustifolia L.) essential oils extracted by supercritical CO 2, hexane and hydrodistillation. *Food and bioprocess technology*, *6*(12), 3481-3489.
- De Melo, D. J., da Silva, M. R., Moliterno, A. A. C., & Zarbin, P. H. G. (2020). Camphor and Borneol as the Male-Produced Sex Pheromone of the Shield Bug, Orsilochides leucoptera (Hemiptera: Scutelleridae). *Journal of Chemical Ecology*, *46*, 490-496.
- Deng, C., Mao, Y., Yao, N., & Zhang, X. (2006). Development of microwave-assisted extraction followed by headspace solid-phase microextraction and gas chromatography–mass spectrometry for quantification of camphor and borneol in Flos Chrysanthemi Indici. Analytica chimica acta, 575(1), 120-125.
- Deng, C., Yao, N., Wang, A., & Zhang, X. (2005). Determination of essential oil in a traditional Chinese medicine, Fructus amomi by pressurized hot water extraction followed by liquid-phase microextraction and gas chromatography–mass spectrometry. *Analytica Chimica Acta*, *536*(1-2), 237-244.
- Dong, L., Wang, J., Deng, C., & Shen, X. (2007). Gas chromatography-mass spectrometry following pressurized hot water extraction and solid-phase microextraction for quantification of eucalyptol, camphor, and borneol in Chrysanthemum flowers. *Journal of separation science*, *30*(1), 86-89.
- Duan M., Y. Xing, J. Guo, H. Chen, R. Zhang (2016). Borneol increases blood-tumour barrier permeability by regulating the expression levels of tight junction-associated proteins Pharm. Biol., 54 (12), 3009-3018

- Evangeline, C., Amor, I.M.V., Rowena, Antemano., Zeebah, Perveen., Gisela, P., Concepcion, M.I., Choudhary, (2007) Cytotoxic C-methylated chalcones from Syzygium samarangense, Pharm. Biol. 45 (10), 777–783.
- Fan, J.G., Farrell, G.C. (2009) Prevention of hepatocellular carcinoma in nonviralrelated liver diseases. *J Gastroen Hepatol*, 24, 712–719.
- Flamini, G., Tebano, M., Cioni, P. L., Ceccarini, L., Ricci, A. S., & Longo, I. (2007). Comparison between the conventional method of extraction of essential oil of Laurus nobilis L. and a novel method which uses microwaves applied in situ, without resorting to an oven. *Journal of Chromatography A*, *1143*(1-2), 36-40.
- Gogus, F., Ozel, M. Z., & Lewis, A. C. (2006). Extraction of essential oils of leaves and flowers of Achillea monocephala by superheated water. *Flavour and fragrance journal*, *21*(1), 122-128.
- Guo, S. S., Yu, L., & Chen, Q. (2008). Progress in pharmacodynamics of Borneol. *Modern Chinese Medicine*. 10(6), 6.
- Han, S., Zheng, H., Lu, Y., Sun, Y., Huang, A., Fei, W., ... & Li, F. (2018). A novel synergetic targeting strategy for glioma therapy employing borneol combination with angiopep-2-modified, DOX-loaded PAMAM dendrimer. *Journal of drug targeting*, *26*(1), 86-94.
- Han, Y. G., Liu, H. L., Zheng, H.J., Li S. G., & Bi, R. C. (2004). Purification and refolding human alpha 5 subunited (PSMA5) of the 20S proteasome, expressed 450 as inclusion bodies in Escherichia coli. *Protein Expr. Purif***,** 35, 360-365.
- Harish, R., Divakar, S., Srivastava, A., & Shivanandappa, T. (2005). Isolation of antioxidant compounds from the methanolic extract of the roots of Decalepis hamiltonii (Wight and Arn.). *Journal of agricultural and food chemistry*, *53*(20), 7709-7714.
- Hatziieremia, S., Gray, A. I., Ferro, V. A., Paul, A., & Plevin, R. (2006). The effects of cardamonin on lipopolysaccharide-induced inflammatory protein production and MAP kinase and NFκB signalling pathways in monocytes/macrophages. *British journal of pharmacology*, *149*(2), 188-198.
- Hur, J., Pak, S. C., Koo, B. S., & Jeon, S. (2013). Borneol alleviates oxidative stress via upregulation of Nrf2 and Bcl-2 in SH-SY5Y cells. *Pharmaceutical biology*, *51*(1), 30-35.
- Hwang, Y. S., Wu, K. H., Kumamoto, J., Axelrod, H., & Mulla, M. S. (1985). Isolation and identification of mosquito repellents in Artemisia vulgaris. *Journal of Chemical Ecology*, *11*(9), 1297-1306.
- Islam, M. S., Wang, C., Zheng, J., Paudyal, N., Zhu, Y., & Sun, H. (2019). The potential role of tubeimosides in cancer prevention and treatment. *European Journal of Medicinal Chemistry*, *162*, 109-121.
- Ji, X., Wang, H., Chen, Y., Zhou, J., & Liu, Y. (2019). Recombinant expressing angiopep-2 fused anti-VEGF single chain Fab (scFab) could cross blood-brain barrier and target glioma. *AMB Express*, *9*(1), 165. https://doi.org/10.1186/s13568-019-0869-3
- Kordali, S., Aslan, I., Çalmaşur, O., & Cakir, A. (2006). Toxicity of essential oils isolated from three Artemisia species and some of their major components to granary weevil, Sitophilus granarius (L.)(Coleoptera: Curculionidae). *Industrial crops and products*, *23*(2), 162-170.
- Kordali, S., Cakir, A., Ozer, H., Cakmakci, R., Kesdek, M., & Mete, E. (2008). Antifungal, phytotoxic and insecticidal properties of essential oil isolated from Turkish Origanum acutidens and its three components, carvacrol, thymol and p-cymene. *Bioresource Technology*, *99*(18), 8788-8795.
- Lai, H., Liu, C., Hou, L., Lin, W., Chen, T., & Hong, A. (2020). TRPM8-regulated calcium mobilization plays a critical role in synergistic chemosensitization of Borneol on Doxorubicin. *Theranostics*, *10*(22), 10154–10170. https://doi.org/10.7150/thno.45861
- Lai, H., Liu, C., Lin, W., & Hong, A. (2020). Chemosensitization of doxorubicin against lung cancer by nature borneol, involvement of TRPM8-regulated calcium mobilization.
- Le, T. X., Ho, A. S. H., Mah, S. H., Wong, T. W., Ong, H. C., Loh, P. H. M., & Lim, Y. M. (2016). Determination of borneol and other chemical compounds of essential oil of Dryobalanops aromatica exudate from Malaysia. *Tropical Journal of Pharmaceutical Research*, *15*(6), 1293-1297.
- Lee, J. H., Jung, H. S., Giang, P. M., Jin, X., Lee, S., Son, P. T., ... & Lee, J. J. (2006). Blockade of nuclear factor-κB signaling pathway and anti-inflammatory activity of cardamomin, a chalcone analog from Alpinia conchigera. *Journal of Pharmacology and Experimental Therapeutics*, *316*(1), 271-278.
- Li, S., Zhou, Y., Wang, R., Zhang, H., Dong, Y., & Ip, C. (2007). Selenium sensitizes MCF-7 breast cancer cells to doxorubicin-induced apoptosis through modulation of phospho-Akt and its downstream substrates. *Molecular cancer therapeutics*, *6*(3), 1031-1038.
- Li, Y. C., Ji, H., Li, X. H., Zhang, H. X., & Li, H. T. (2017). Isolation of nematicidal constituents from essential oil of Kaempferia galanga L rhizome and their activity against Heterodera avenae Wollenweber. *Tropical Journal of Pharmaceutical Research*, *16*(1), 59-65.
- Lipinska, N., Romaniuk, A., Paszel-Jaworska, A., Toton, E., Kopczynski, P., & Rubis, B. (2017).

Telomerase and drug resistance in cancer. *Cellular and Molecular Life Sciences*, *74*(22), 4121-4132.

- Liu W.J., Y.B. Yin, J.Y. Sun, S. Feng, J.K. Ma, X.Y. F u, Y.J. Hou, M.F. Yang, B.L. Sun, C.D., Fan. (2018), Natural borneol is a novel chemosensitizer that enhances temozolomide-induced anticancer efficiency against human glioma by triggering mitochondrial dysfunction and reactive oxide species-mediated oxidative damage Oncotargets Ther., 11, 5429-5439
- Liu, Q., Shang, F., Guo, W., Hobbs, M., Valverde, P. Reddy, V., Taylor, A. (2004). Regulation of the ubiquitin proteasome pathway in human lens epithelial cells during 457 the cell cycle. *Exp. Eye. Res*., 78, 197-205.
- Liu, W. J., Yin, Y. B., Sun, J. Y., Feng, S., Ma, J. K., Fu, X. Y., ... & Fan, C. D. (2018). Natural borneol is a novel chemosensitizer that enhances temozolomide-induced anticancer efficiency against human glioma by triggering mitochondrial dysfunction and reactive oxide species-mediated oxidative damage. *OncoTargets and therapy*, *11*, 5429.
- Lv, L., Li, X., Qian, W., Li, S., Jiang, Y., Xiong, Y., & Xin, H. (2020). Enhanced Anti-Glioma Efficacy by Borneol Combined With CGKRK-Modified Paclitaxel Self-Assembled Redox-Sensitive Nanoparticles. *Frontiers in pharmacology*, *11*, 558.
- Mehmood, T., Maryam, A., Ghramh, H. A., Khan, M., & Ma, T. (2017). Deoxyelephantopin and isodeoxyelephantopin as potential anticancer agents with effects on multiple signaling pathways. *Molecules*, *22*(6), 1013.
- Meng, X., Dong, X., Wang, W., Yang, L., Zhang, X., Li, Y., ... & Su, J. (2018). Natural borneol enhances paclitaxel-induced apoptosis of ESCC cells by inactivation of the PI3K/AKT. *Journal of food science*, *83*(5), 1436-1443.
- Meng, L., Chu, X., Xing, H., Liu, X., Xin, X., Chen, L., & Gao, Z. (2019). Improving glioblastoma therapeutic outcomes via doxorubicin-loaded nanomicelles modified with borneol. *International journal of pharmaceutics*, *567*, 118485.
- Meng, X., Dong, X., Wang, W., Yang, L., Zhang, X., Li, Y., & Su, J. (2018). Natural Borneol Enhances Paclitaxel Induced Apoptosis of ESCC Cells by Inactivation of the PI3K/AKT. *Journal of food science*, *83*(5), 1436-1443.
- Mitin V.V., E.A. Ivanova, P.E. Prokhorova, Yu. Yu, Morzherin, (2016) Chlorophenols in organic synthesis, Chimica Techno Acta 3 (3) 164–192.
- Müller, U. S., Wirth, W., Junge-Hülsing, G., & Hauss, W. H. (1973). Suppressive effects in mesenchyme and immunosuppressive effects of cytostatica. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, *7*(2), 228-233.
- Nageen, B., Sarfraz, I., Rasul, A., Hussain, G., Rukhsar, F., Irshad, S., ... & Ali, M. (2020). Eupatilin: a natural pharmacologically active flavone compound with its wide range applications. *Journal of Asian natural products research*, *22*(1), 1-16.
- Newman, D. J., & Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014. *Journal of natural products*, *79*(3), 629-661.
- Niedzwiecki, A., Roomi, M. W., Kalinovsky, T., & Rath, M. (2016). Anticancer efficacy of polyphenols and their combinations. *Nutrients*, *8*(9), 552.
- Nishimura, O. (1995). Identification of the characteristic odorants in fresh rhizomes of ginger (Zingiber officinale Roscoe) using aroma extract dilution analysis and modified multidimensional gas chromatography-mass spectroscopy. *Journal of Agricultural and Food Chemistry*, *43*(11), 2941-2945.
- Okoh, O. O., Sadimenko, A. P., & Afolayan, A. J. (2010). Comparative evaluation of the antibacterial activities of the essential oils of Rosmarinus officinalis L. obtained by hydrodistillation and solvent free microwave extraction methods. *Food chemistry*, *120*(1), 308-312.
- Qi, H. P., Gao, X. C., Zhang, L. Q., Wei, S. Q., Bi, S., Yang, Z. C., & Cui, H. (2013). In vitro evaluation of enhancing effect of borneol on transcorneal permeation of compounds with different hydrophilicities and molecular sizes. *European journal of pharmacology*, *705*(1-3), 20-25.
- Quispe-Condori, S., Sánchez, D., Foglio, M. A., Rosa, P. T., Zetzl, C., Brunner, G., & Meireles, M. A. A. (2005). Global yield isotherms and kinetic of artemisinin extraction from Artemisia annua L leaves using supercritical carbon dioxide. *The Journal of supercritical fluids*, *36*(1), 40-48.
- Rabi, T., Bishayee, A. (2009). Terpenoids and breast cancer chemoprevention. *Breast Cancer Res Treat.* 115, 223-39.
- Ramezani, M., Hatamipour, M., & Sahebkar, A. (2018). Promising anti-tumor properties of bisdemethoxycurcumin: A naturally occurring curcumin analogue. *Journal of cellular physiology*, *233*(2), 880-887.
- Rayman, MP. (2005) Selenium in cancer prevention: a review of the evidence and mechanism of action. *P Nutr Soc* 64, 527–542.
- Rivett, D. E. A. (1971). The isolation of tricyclenal and borneol from Asparagus thunbergianus Schult. *South African Journal of Chemistry*, *24*(1), 87-90.
- Sen T., S.K. Samanta. (2015) Medicinal plants, human health and biodiversity: a broad review, Adv. Biochem. Eng. *Biotechnol.* 147 59–110.

- Shi, M., Cai, Q., Yao, L., Mao, Y., Ming, Y., & Ouyang, G. (2006). Antiproliferation and apoptosis induced by curcumin in human ovarian cancer cells. *Cell biology international*, *30*(3), 221-226.
- Su, J., H. Lai, J. Chen, L. Li, Y.S. Wong, T. Chen, X. L i (2013). Natural borneol, a monoterpenoid compound, potentiates selenocystine-induced apoptosis in human hepatocellular carcinoma cells by enhancement of cellular uptake and activation of ROS-mediated DNA damage *PLoS One*, 8 (5) Article e63502
- Su, J., Lai, H., Chen, J., Li, L., Wong, Y. S., Chen, T., & Li, X. (2013). Natural borneol, a monoterpenoid compound, potentiates selenocystine-induced apoptosis in human hepatocellular carcinoma cells by enhancement of cellular uptake and activation of ROS-mediated DNA damage. *PLoS One*, *8*(5), e63502.
- Tabanca, N., Kırımer, N., Demirci, B., Demirci, F., & Başer, K. H. C. (2001). Composition and antimicrobial activity of the essential oils of Micromeria cristata subsp. phrygia and the enantiomeric distribution of borneol. *Journal of Agricultural and Food chemistry*, *49*(9), 4300-4303.
- Tang, B., Fang, G., Gao, Y., Liu, Y., Liu, J., Zou, M., ... & Cheng, G. (2015). Lipid-albumin nanoassemblies co-loaded with borneol and paclitaxel for intracellular drug delivery to C6 glioma cells with P-gp inhibition and its tumor targeting. *asian journal of pharmaceutical sciences*, *10*(5), 363-371.
- Teixeira, S., Mendes, A., Alves, A., & Santos, L. (2007). Simultaneous distillation–extraction of high-value volatile compounds from Cistus ladanifer L. *Analytica chimica acta*, *584*(2), 439-446.
- Umano, K., Hagi, Y., Nakahara, K., Shoji, A., & Shibamoto, T. (2000). Volatile chemicals identified in extracts from leaves of Japanese mugwort (Artemisia princeps Pamp.). *Journal of Agricultural and Food Chemistry*, *48*(8), 3463-3469.
- Wang, R., Wang, R., & Yang, B. (2009). Extraction of essential oils from five cinnamon leaves and identification of their volatile compound compositions. *Innovative Food Science & Emerging Technologies*, *10*(2), 289-292.
- Wang, Y., Wang, A., Tian, H., Wang, H., & Zou, C. (2014). Determination of (-)-Borneol, Camphor and Isoborneol in Blumea balsamifera (L.) DC. Leaves by Simultaneous Ultrasonic and Microwave Assisted Extraction and Gas Chromatography. *Asian Journal of Chemistry*, *26*(4), 997.
- Watanabe, K., & Shimizu, N. (2017). Identification of a sex pheromone of the chrysanthemum lace bug Corythucha marmorata (Hemiptera: Tingidae). *Scientific reports*, *7*(1), 1-8.
- Wei, W., Azhar Rasul, A. S., Sarfraz, I., Hussain, G., Nageen, B., Liu, X., ... & Li, J. (2019). Curcumol: from plant roots to cancer roots. *International journal of biological sciences*, *15*(8), 1600-1609.
- Wenqiang, G., Shufen, L., Ruixiang, Y., & Yanfeng, H. (2006). Comparison of composition and antifungal activity of Artemisia argyi Levl. et Vant inflorescence essential oil extracted by hydrodistillation and supercritical carbon dioxide. *Natural Product Research*, *20*(11), 992-998.
- Wijdeven, R.H., Pang, B., Assaraf, Y. G., & Neefjes, J. (2016). Old drugs, novel ways out: Drug resistance toward cytotoxic chemotherapeutics. *Drug Resistance Updates*, *28*, 65-81.
- Wu, J., Xie, J., Zhang, Q. L., Lin, Z. X., Xie, H., & Sun, B. (2016). Research progress on meridian-guiding theory of traditional Chinese medicine. *Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica*, *41*(13), 2428-2434.
- Xiao, Y. Z., Chen, Z. P., & Ping, Q. N. (2009). Study on the absorption promoting effect of Borneol on Ligustrazine. *Acta pharmacology*, *44*(8), 915-921.
- Xu, H., Ju, D., Jarois, T., Xie,Y. (2008) Diminished feedback regulation of proteasome expression and resistance to proteasome inhibitors in breast cancer cells. *Breast Cancer Res. Treat*, 107, 267-274.
- Yang Y. L., Ji C., Cheng L., He L., C. C. Lu, R. Wang and Z. G. Bi, Cancer Sci., 2012, 103, 1538–1545.
- Yang, Z., An, W., Liu, S., Huang, Y., Xie, C., Huang, S., & Zheng, X. (2020). Mining of candidate genes involved in the biosynthesis of dextrorotatory borneol in Cinnamomum burmannii by transcriptomic analysis on three chemotypes. *PeerJ*, *8*, e9311.
- Yang, Z., Guo, P., Han, R., Wu, S., & Gao, J. M. (2018). Gram scale separation of borneol and camphor from Cinnamomum camphora (L.) Presl by continuous counter current chromatography. *Separation Science Plus*, *1*(2), 144-153.
- Ye, Q., and Deng, C. (2008) Determination of camphor and borneol in traditional Chinese medicines by microwave-assisted extraction and gas chromatography with flame ionization detector, *Analytical letters*, *41*(13), 2387-2401.
- Yuan, R., Huang, Y., Chan, L., He, D., & Chen, T. (2020). Engineering EHD1-Targeted Natural Borneol Nanoemulsion Potentiates Therapeutic Efficacy of Gefitinib against Nonsmall Lung Cancer. *ACS Applied Materials & Interfaces*, *12*(41), 45714-45727.

- Zhang, W., & Qiu, T. (2010). Extraction of natural D-borneol by ultrasound enhanced distillation. *Modern Food Science and Technology*, *26*(8), 834-846.
- Zhong, Z., Yu, H., Wang, S., Wang, Y., & Cui, L. (2018). Anti-cancer effects of Rhizoma Curcumae against doxorubicin-resistant breast cancer cells. *Chinese medicine*, *13*(1), 1-10.
- Zou, L., Di Wang, Y. H., Fu, C., Li, W., Dai, L., Yang, L., & Zhang, J. (2017). Drug resistance reversal in ovarian cancer cells of paclitaxel and borneol combination therapy mediated by PEG-PAMAM nanoparticles. *Oncotarget*, *8*(36), 60453.